PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 401/06, A61K 31/495, C07D 401/12, 295/12, 241/04, 401/14, 405/12, A61K 31/44, C07D 409/06, 417/06

A1

(11) International Publication Number: **WO 96/31501**

(43) International Publication Date: 10 October 1996 (10.10.96)

(21) International Application Number: PCT/US96/04169

(22) International Filing Date: 3 April 1996 (03.04.96)

(30) Priority Data:
08/418,319 7 April 1995 (07.04.95) US

(71) Applicants: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). PHARMACOPEIA, INC. [US/US]; 101 College Road East, Princeton, NJ 08540 (US).

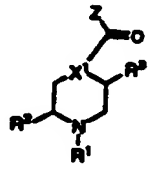
(72) Inventors: DOLL, Ronald, J.; 126 Union Avenue, Maplewood, NJ 07040 (US). MALLAMS, Alan, K.; 147 Kings Highway, Hackettstown, NJ 07840 (US). AFONSO, Adriano; 10 Woodmere Road, West Caldwell, NJ 07006 (US). RANE, Dinanath, F.; 2 Hayground Court, Morganville, NJ 07751 (US). NJOROGE, F., George; 2597 Juliat Place, Union, NJ 07083 (US). ROSSMAN, Randall, A.; 82 Oakley Terrace, Nutley, NJ 07110 (US). BALDWIN, John, J.; 621 Gypsy Hill Circle, Gwynedd Valley, PA 19437 (US). LI, Ge; 27 Marco Polo Court, Franklin Park, NJ 08823 (US). READER, John, C.; 112 Biscayne Court #8, Princeton, NJ 08540 (US).

(74) Agents: MAJKA, Joseph, T. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

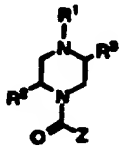
(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

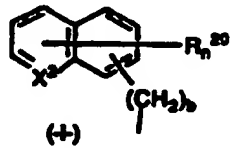
(54) Title: CARBONYL-PIPERAZINYL AND PIPERIDINIL COMPOUNDS WHICH INHIBIT FARNESYL PROTEIN TRANSFERASE



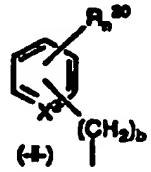
(1.0)



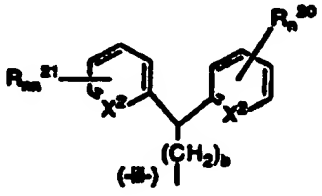
(1.1)



(I)



(II)



(III)

(57) Abstract

Novel carbonyl piperazinyl and piperidinyl compounds of formula (1.0) or (1.1) and pharmaceutical compositions are disclosed. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel carbonyl piperazinyl or piperidinyl compound to a biological system. In particular, the method inhibits the abnormal growth cells in a mammal such as the human being. A compound of formula (1.0) and (1.1) or a pharmaceutically acceptable salt or solvate thereof, wherein Z is a group which is (i), (ii) or (iii), wherein X1 is CH or N; X2 can be the same or different and can be CH, N, or N-O; b is 0, 1, 2, 3, 4; n and nn independently represent 0, 1, 2, 3, 4 or when X2 is CH, n and nn can be 5; R20 and R21, R1, R2 and R3 are as given in the description.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

CARBONYL-PIPERAZINYL AND PIPERIDINIL COMPOUNDS WHICH INHIBIT FARNESYL PROTEIN TRANSFERASE

BACKGROUND

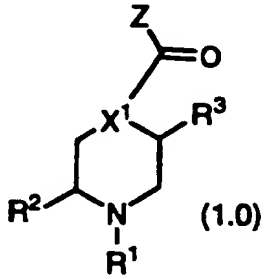
Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be additional compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

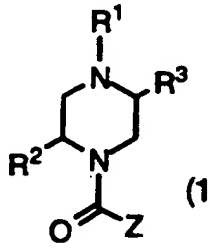
SUMMARY OF THE INVENTION

The present invention is directed to novel carbonyl piperazinyl and piperidinyl compounds of the formula:



(1.0)

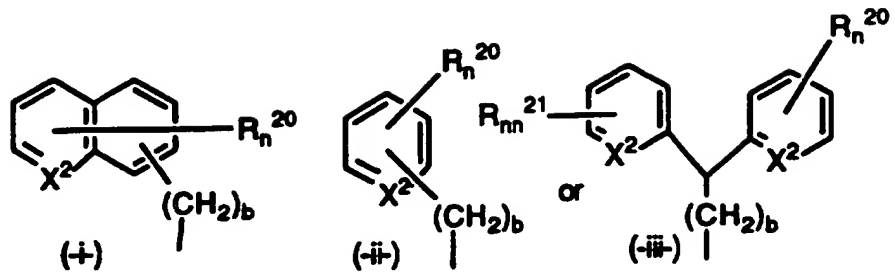
and



(1.1)

or a pharmaceutically acceptable salt or solvate th reof, wherein:

(1) Z is a group which is:



wherein X^1 is CH or N;

X^2 can be the same or different and can be CH, N or N-O;

b is 0, 1, 2, 3 or 4;

n and nn independently represent 0, 1, 2, 3, 4 or when X^2 is CH, n and nn can be 5;

R^{20} and R^{21} can be the same group or different groups when n or nn is 2, 3, 4 or 5, and can be:

(a) hydrogen, C_1 to C_6 alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, wherein each of said C_1 to C_6 alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl can be optionally substituted with one or more of the following:

C_1 to C_4 alkyl, C_3-C_6 cycloalkyl,
$(CH_2)_tOR^8$ wherein t is 0, 1, 2, 3 or 4,
$(CH_2)_tNR^8R^9$ wherein t is 0, 1, 2, 3 or 4, or
halogen;

(b) C_3 to C_6 cycloalkyl; (c) $-OR^8$; (d) $-SR^8$; (e) $-S(O)R^8$;

(f) $-SO_2R^8$; (g) $-NR^8R^9$; (h) -CN; (i) $-NO_2$,

(j) $-CF_3$ or (k) halogen (l) $-CONR^8R^9$ or (m) $-COR^{13}$

wherein R^8 and R^9 can independently represent:

H, C_1 to C_4 alkyl, C_3 to C_6 cycloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, aryl or aralkyl and each of said alkyl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, aryl or aralkyl can be optionally substituted with one to three of the following:

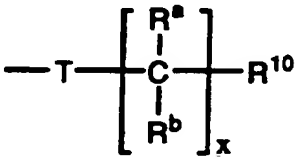
C_1 to C_4 alkoxy, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, halogen, -OH, $-C(O)R^{13}$, $-NR^{14}R^{15}$;
$-CONR^8R^9$ or $-N(R^8)COR^{13}$; -CN; C_3-C_6 cycloalkyl, $S(O)_qR^{13}$;
or C_3-C_{10} alkoxyalkoxy wherein q is 0, 1 or 2;
wherein R^{13} is select d from C_1 to C_4 alkyl, aryl or aralkyl, and

R^{14} and R^{15} are independently selected from H, C_1 to C_4 alkyl or aralkyl;

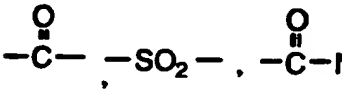
and optionally, when R^8 and R^9 are bound to the same nitrogen, R^8 and R^9, together with the nitrogen to which th y are bound, can form a 5 to 7 membered heterocycloalkyl ring which may optionally contain O, NR^8, S(O)q wherein q is 0, 1 or 2;

with the proviso that R^8 is not H in substituents (e) and (f) , and with the proviso that R^8 or R^9 is not $-CH_2OH$ or $-CH_2NR^{14}R^{15}$ when R^8 or R^9 is directly attached to a heteroatom;

(2) R^1 is a group which is:



wherein

T can be  , or a single bond,

x = 0, 1, 2, 3, 4, 5 or 6,

R^a and R^b independently represent H, aryl, alkyl, amino, alkylamino, alkoxy, aralkyl, heterocycloalkyl, $-COOR^{16}$, $-NH(CO)_zR^{16}$ wherein z = 0 or 1, $-(CH_2)_wS(O)_mR^{16}$ wherein w=0, 1, 2 or 3 such that when x is greater than 1, then R^a and R^b can be independent of the substituents on an adjacent carbon atom provided R^a and R^b are not both selected from alkoxy, amino, alkylamino, and $-NH(CO)_zR^{16}$;

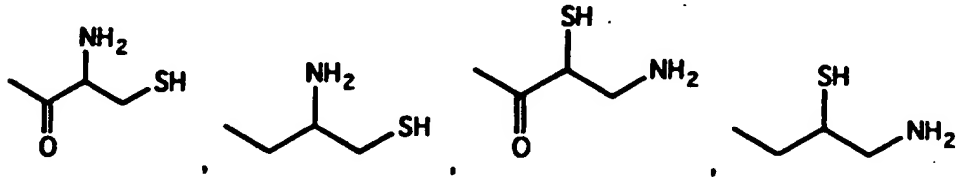
m = 0, 1 or 2 wherein

R^{16} represent H, alkyl, aryl or aralkyl,

or R^a and R^b taken together can represent cycloalkyl, =O, =N-O-alkyl or heterocycloalkyl, and

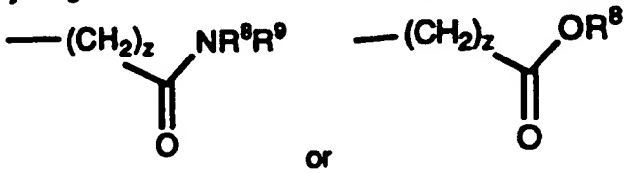
R^{10} can represent H, alkyl, aryl, aryloxy, arylthio, aralkoxy, aralkthio, aralkyl, heteroaryl, heterocycloalkyl,

or R^1 can also be



r disulfide dimers thereof;

(3) R^2 and R^3 are independently selected from th group which is:
hydrogen, C_1 to C_8 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl,



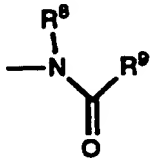
;

wherein z is 0, 1, 2, 3 or 4; and said alkyl, alkenyl, or alkynyl group is optionally substituted with one or more groups which can independently represent:

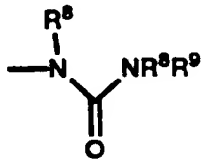
(a) aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, wherein each of said aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl group can be optionally substituted with one or more of the following:

C_1 to C_4 alkyl,
$(CH_2)_tOR^8$ wherein t is 0, 1, 2, 3 or 4,
$(CH_2)_tNR^8R^9$ wherein t is 0, 1, 2, 3 or 4, or
halogen;

(b) C_3 to C_6 cycloalkyl; (c) $-OR^8$; (d) $-SR^8$; (e) $-S(O)R^8$;
(f) $-SO_2R^8$; (g) $-NR^8R^9$; (h)

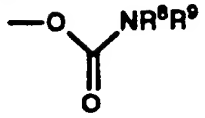


(i)

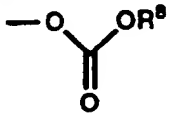


;

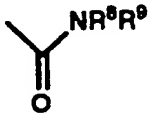
(j)



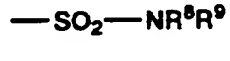
; (k)



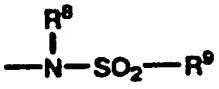
; (l)



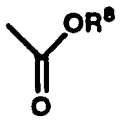
; (m)



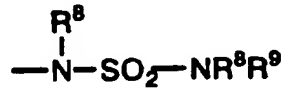
; (n)



(o)

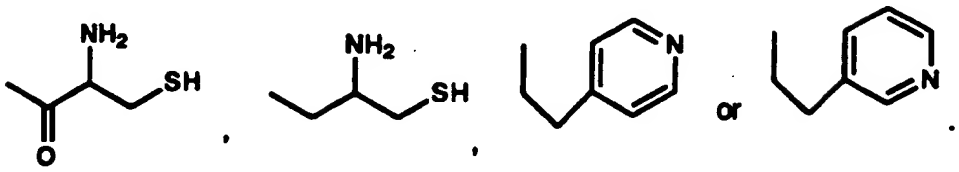


or (p)



wherein R^8 and R^9 are defined hereinbefore; and
and optionally, when R^8 and R^9 are bound to the same nitrogen, R^8 and R^9, together with the nitrogen to which they are bound, can form a 5 to 7 membered heterocycloalkyl ring which may optionally contain O, NR^8, S(O)q wherein q is 0, 1 or 2;
with the proviso that for compound (1.0) wh n X^1 is CH, then R^3 is hydrogen, and with the further proviso that R^2 and R^3 cannot both be hydrogen;

and with the provision that when X^1 is N, then R^1 is not



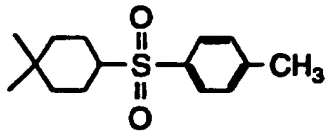
One skilled in the art will recognize that compound (1.0) and (1.1) are identical when R^2 and R^3 are the same. One skilled will also recognize that compounds (1.0) and (1.1) are positional isomers when R^2 is different from R^3. In the present specification, the procedures described herein for preparing compound (1.0) are also applicable for preparing compound (1.1).

Preferably, R^3 is H; b is 0; or R^3 is H and b is 0.

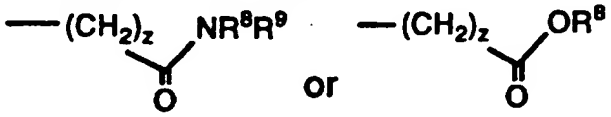
Also preferred is that Z is (-i-), (-ii-) or (-iii-), X^2 is CH or N, b=0 or 1, R^{20} is H, C1-C6 alkyl or halo, n = 0 or 1;

X^1 is N;

for R^1, T is -CO-, $-SO_2-$ or a single bond, and R^a and R^b independently represent H or C_1-C_6 alkoxy or R^a and R^b taken together can form C_3-C_6 cycloalkyl, =N-O-

C1-C6 alkyl or 

R^{10} is H, aryl, arylthio or heteroaryl;

R^2 is H, 

z = 0 or 1, R^8 is H and R^9 is alkyl, cycloalkyl, aralkyl, heterocycloalkyl or substituted alkyl; and

R^3 is hydrogen.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes th abnormal growth of: (1) tumor cells (tumors) xpressing an

activated Ras oncogene; (2) tumor cells in which th Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras protein. Without wishing to be bound by theory, it is believed that these compounds may function either through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer, or through inhibition of ras farnesyl protein transferase, thus making them useful for their antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells. Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene. Alternatively, compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein, to a mammal (.g.,

a human) in need of such tr atment. For xample, the benign prolif rative disorder neurofibromatosis, or tumors in which Ras is activat d du to mutation or overexpression of tyrosine kinase oncogenes (.g., neu, src, abl, lck, and fyn), may be inhibited by the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein.

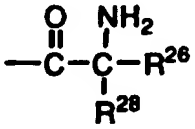
In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

Ac - represents acetyl;

acyl radical of a naturally occurring amino acid - represents a group of the formula $-C(O)C(NH_2)R^{26}R^{28}$, i.e.:



wherein R^{26} and R^{28} represent the substituents of an amino acid bound to the α-carbon; for example R^{26} and R^{28} can be independently selected from H, alkyl, or alkyl substituted with an R^{30} group, wherein R^{30} can be, for example, -OH, SH, $-SCH_3$, $-NH_2$, phenyl, p-hydroxyphenyl, indolyl or imidazolyl, such that $HO-C(O)C(NH_2)R^{26}R^{28}$ is an amino acid selected from, for example, alanine, cysteine, cystine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, tryptophane, tyrosine or valine. Preferably the stereochemistry of the amino acid is of the L absolute configuration.

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms; for example methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; wherein said alkyl group may be optionally and independently substituted with one two or three of hydroxy, alkoxy, halo (e.g. CF_3), amino, alkylamino, dialkylamino, N-acylalkylamino, N-alkyl-N-acylamino, $-S(O)_m$-alkyl where m=0, 1 or 2 and alkyl is defined above;

alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and th like.

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

aq - represents aqueous

aralkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been replaced by one or more aryl groups, as defined below (e.g., benzyl, diphenylmethyl);

aryl (including the aryl portion of aryloxy and aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is phenyl or napthyl), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally and independently substituted with one, two, three or more of halo, C1-C6 alkyl, C1-C6 alkoxy, amino, alkylamino, dialkylamino, aryl, aralkoxy, aryloxy, $-NO_2$, $-S(O)_m$-aryl wherein m=0, 1 or 2, $C(O)R^{11}$ (wherein R11 is as defined hereinbefore), an acyl radical, $-COOR^{16}$ (wherein R^{16} represents H, alkyl, aryl or aralkyl), or substituted C1-C6 alkyl wherein the alkyl group is substituted with one two or three of amino, alkylamino, dialkylamino, aryl, N-acylalkylamino, N-alkyl-N-acylamino, N-aralkyl-N-acylamino, hydroxy, alkoxy, halo, or heterocycloalkyl, provided that when there are two or more hydroxy, amino, alkylamino or dialkylamino substituents on the substituted C_1-C_6 alkyl group, the substituents are on different carbon atoms; or alternatively said aryl group may be fused through adjacent atoms to form a fused ring containing up to four carbon and/or heteroatoms (e.g. methylene dioxyphenyl, indanyl, tetralinyl, dihydrobenzofuranyl);

aralkoxy - represents an aralkyl group, as defined above, in which the alkyl moiety is covalently bonded to an adjacent structural element through an oxygen atom, e.g. benzyloxy;

aryloxy - represents an aryl group, as defined above, covalently bonded to an adjacent structural element through an oxygen atom, e.g, phenoxy;

arylthio - represents an aryl group, as defined abov , covalently bonded to an adjacent structural elem nt through a sulfur atom, for example, ph nylthio;

BOC - represents tert-butoxycarbonyl;

BOC-ON - represents [2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile];

C - represents carbon;

CBZ - represents benzyloxycarbonyl;

CPh_3 - represents triphenylmethyl;

cycloalkyl-represents a saturated carbocyclic ring, branched or unbranched, of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

DBU - represents 1,8-diazabicyclo[5.4.0]undec-7-ene;

DCC - represents dicyclohexylcarbodiimide;

DCM - represents dichloromethane;

DIC - represents diisopropylcarbodiimide;

DMAP - represents 4-dimethylaminopyridine;

DMF - represents N,N-dimethylformamide;

EDC (also DEC) - represents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride;

FMOC - represents 9-fluorenylmethyoxycarbonyl;

FMOC-Cl - represents 9-fluoroenylmethyl chloroformate;

HATU - represents [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate];

MCPBA - represents m-chloroperbenzoic acid;

Ph - represents phenyl;

TBAF - represents tetrabutylammonium fluoride;

TFA - represents trifluoroacetic acid;

THF - represents tetrahydrofuran;

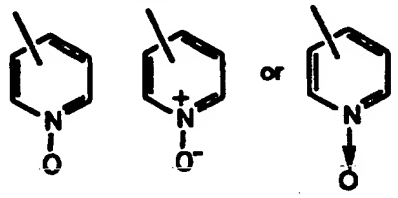
halogen (halo)-represents fluoro, chloro, bromo and iodo;

haloalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more halogen atoms, ie. chloromethyl and trifluromethyl;

heterocycloalkyl-represents a saturated, branched or unbranched mono-, bi- or tricyclic carbocylic ring(s) containing from 3 to 15 carbon atoms in each ring, preferably from 4 to 6 carbon atoms, wherein at least one carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from -O-, -S- or -N- (suitable heterocycloalkyl groups include 2- or 3-tetrahydrofuranyl, 2- or 3-tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 1-,2- or 3-morpholino, 2- or 3-piperizinyl, 2- r 4-dioxanyl, diaza-2,2,2-bicyclooctane etc.); with any of the available substitutable carbon and nitrogen atoms in the ring

being optionally and independently substitut d with one, two, three or more of C_1-C_6 alkyl, aryl, aralkyl, haloalkyl, amino, alkylamino, dialkylamino, -$S(O)_m$-aryl where m=0, 1 or 2 and aryl is defined above, -$C(O)R^{11}$ wherein R^{11} is defined abov or an acyl radical of a naturally occuring amino acid;

heteroaryl-represents cyclic groups having one, two or three heteroatom selected from -O-, -S- or -N-, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., quinolinyl, imidazolyl, furanyl, triazolyl, thiazolyl, indolyl, benzothienyl, 2- or 3- thienyl, 1-, 2-, 3- or 4-pyridyl or pyridyl N-oxide, wherein pyridyl N-oxide can be represented as:



with all available substitutable carbon and heteroatoms of the cyclic group being intended as possible points of attachment, said cyclic group being optionally and independently substituted with one, two, three or more of halo, alkyl, aryl, aralkyl, heteroaryl, hydroxy, alkoxy, phenoxy, -NO_2, CF_3, amino, alkylamino, dialkylamino, and -$COOR^{16}$ wherein R^{16} represents H, alkyl, aryl or aralkyl (e.g., benzyl);

heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by heteroaryl groups (as defined above);

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain compounds (1.0) will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the lik .

Certain basic compounds (1.0) can also form pharmaceutically acceptabl salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

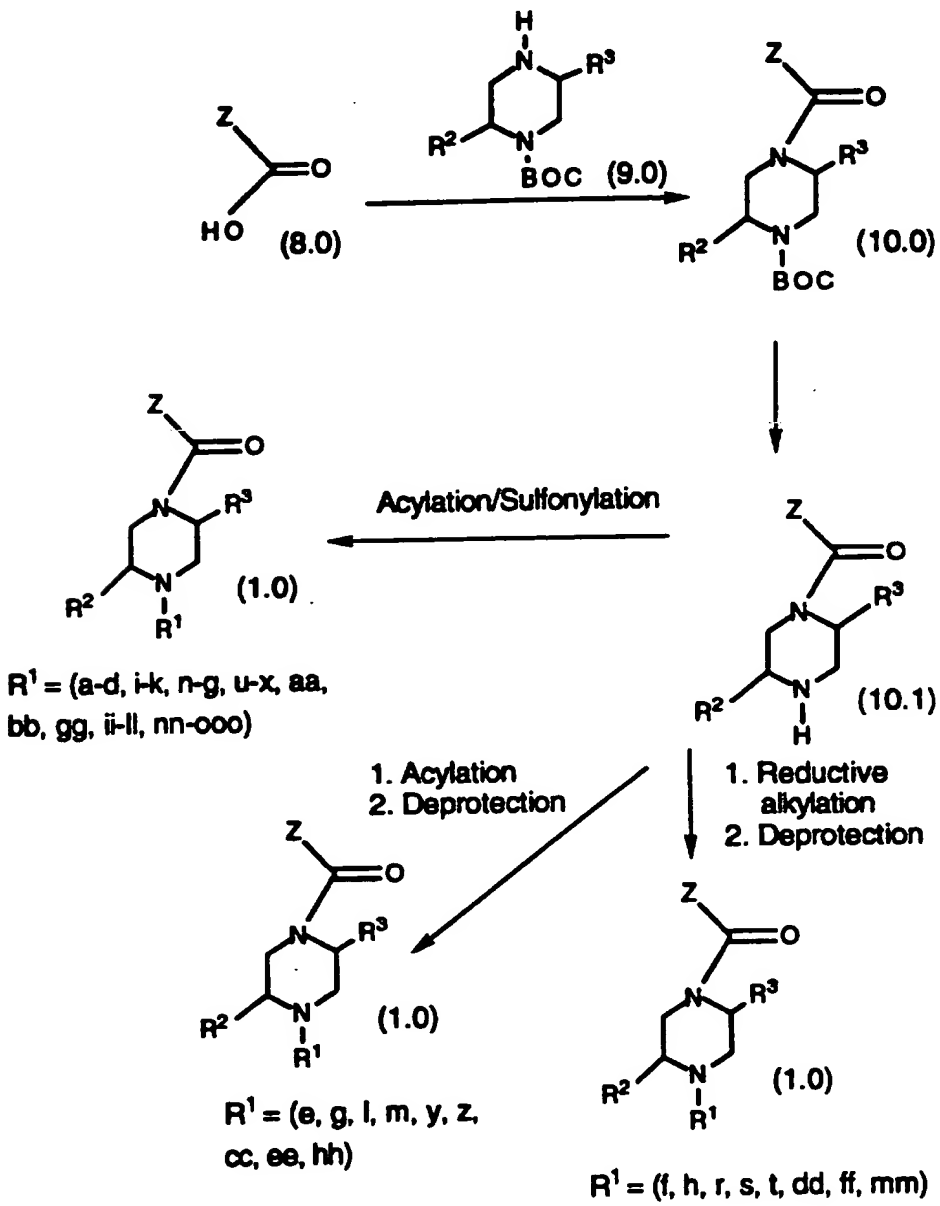
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The following processes may be employed to produce compounds of the invention. Various intermediates in the processes described below can be produced by methods known in the art, see for example, U.S. 3,409,621, U.S. 5,089,496, WO89/10369, WO92/20681, and WO93/02081, the disclosures of each being incorporated herein by reference thereto.

A. Process A for Preparing Piperazinyl Compounds and Starting Materials.

The piperazinyl compounds of th present invention and starting materials thereof, can be prepared according to th following overall Process A.

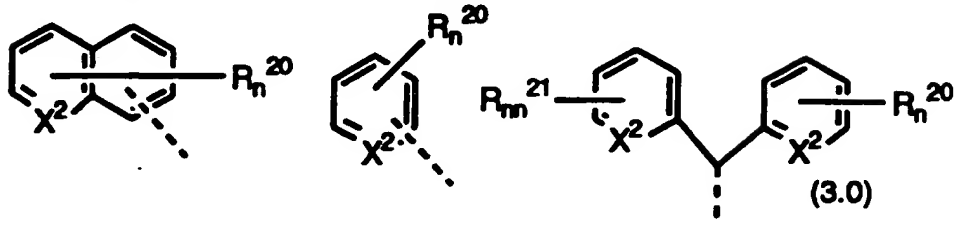
Process A



wherein Z, BOC, R^1, R^2 and (a-ooo) are as defined herein.

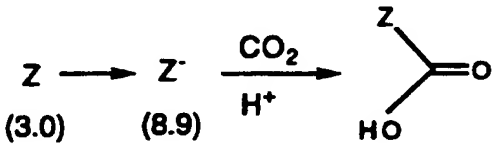
A1. Preparation of Piperazinyl Starting Materials.

The aromatic compounds ("Z") of formula (3.0)



(3.0)

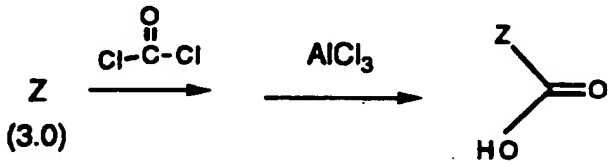
wherein R_n^{20}, R_{nn}^{21} and X^2 are as defined hereinbefore, and the solid floating bond indicates that R_n^{20} and R_{nn}^{21} can be bonded to the aromatic ring at any suitable atom for attachment, ie.carbon, are known to those skilled in the art. The dotted floating bond indicates the subsequent site of introduction for the carboxyl group.



(8.0)

Using a reaction such the Kolbe-Schmidt Reaction, the carboxylic acids of formula (8.0) can be prepared by contacting the aromatic compounds of formula (3.0) with a base such as n-butyl lithium, followed by treatment with carbon dioxide, followed then by treatment with a suitable acid, such as hydrochloric acid, to give carboxylic acid (8.0), which are also compounds known in the art.

Alternatively, carboxylic acid (8.0), wherein b=0, can be prepared by reacting the aromatic halide (i.e.R^{20} is halo) of compound (3.0) and an organometallic such as n-butyl lithium to yield aromatic anion (8.9), which is then treated with carbon dioxide and acid as described above, to give carboxylic acid (8.0).

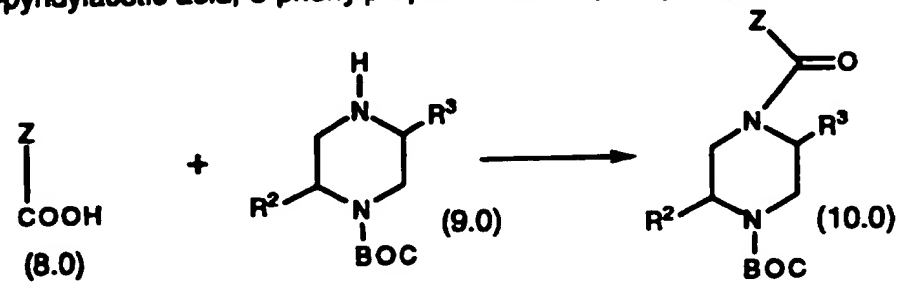


(8.0)

In an alternative reaction, carboxylic acids (8.0) can be pr pared by reacting aromatic compounds (3.0) with phosgene in the presence of a Lewis Acid, such as

aluminum chloride ($AlCl_3$) followed by hydrolysis of th acid chloride to giv carboxylic acid (8.0).

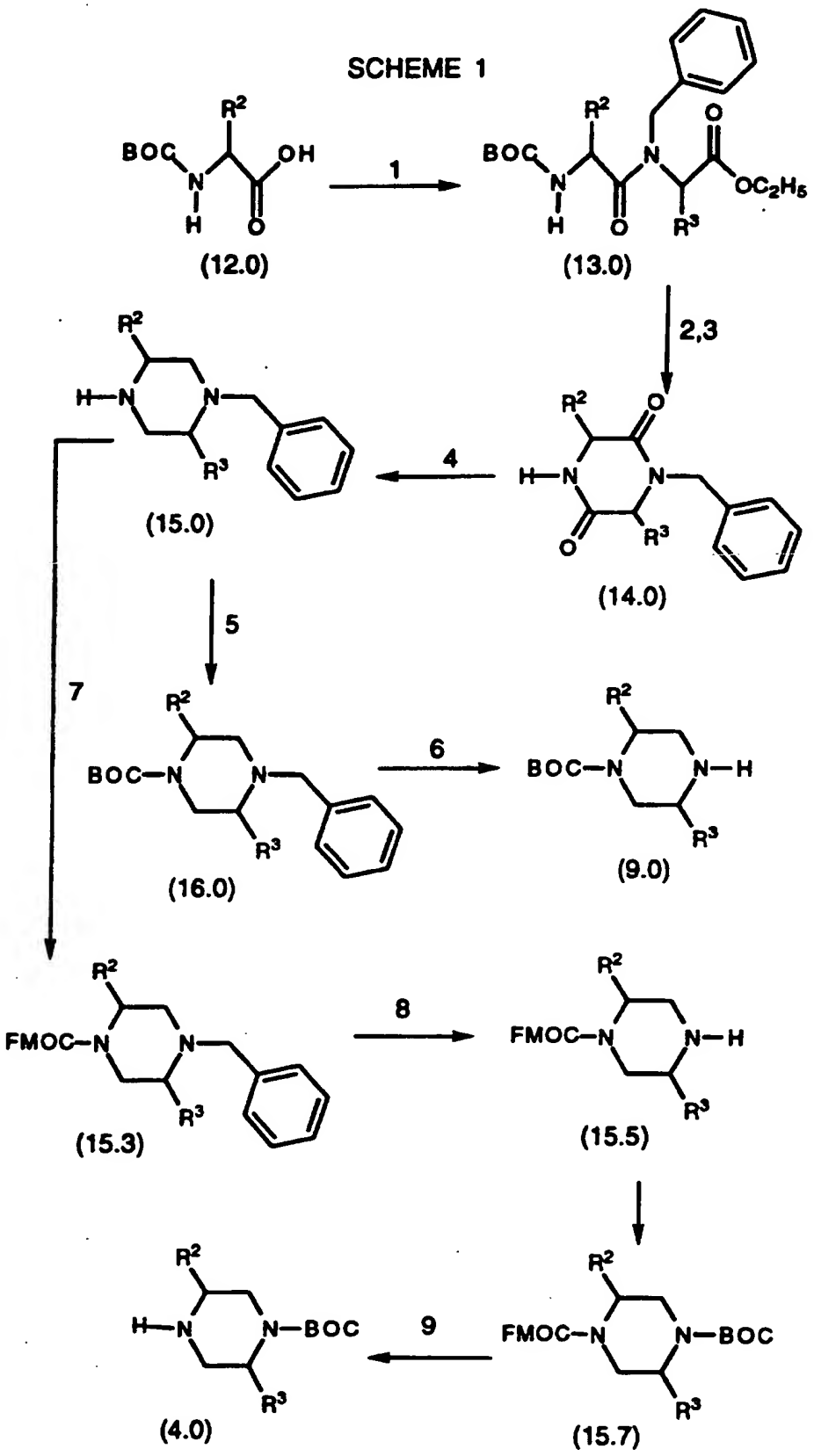
Also, carboxylic acids (8.0) wherein b=1, 2, 3 or 4 are also known in the art, e.g. 3-pyridylacetic acid, 3-phenylpropionic acid, 4-phenylbutyric acid and th lik .



The carboxylic acid (8.0) is then reacted with piperazinyl intermediate (9.0) in the presence of a coupling reagent (such as a carbodiimide, e.g., dicyclohexylcarbodiimide) in a suitable solvent such as DMF at a suitable temperature to produce the piperazinyl amide (10.0).

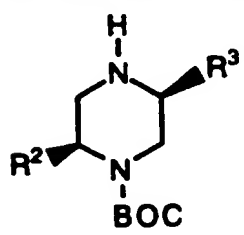
The preparation of compounds of Formula 9.0 is described in WO 95/00497, published January 5, 1995, the disclosure of which is incorporated herein by reference thereto. The preparation of piperazinyl intermediate (9.0) is depicted in Schemes 1 and 2.

SCHEME 1

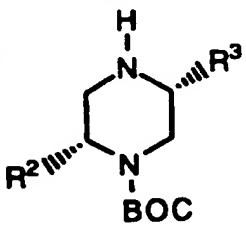

BOC
OH
R2
1
OC2H5
R3
(12.0)
(13.0)
2,3
4
(15.0)
(14.0)
5
7
6
(16.0)
(9.0)
FMOC
8
(15.3)
(15.5)
9
(4.0)
(15.7)

Scheme 1 describes the synthesis of 2,3-disubstituted piperazines wherein R^2 and R^3 independently represent H, alkyl, alkenyl, or alkynyl. Scheme 1 also describes the synthesis of 2,3-disubstituted piperazines wherein R^2 and R^3 independently represent is alkyl, alkenyl, or alkynyl which are substituted with substituent groups (a), (b), (c), (d) and (g) as defined above, with the exception that R^8 and R^9 cannot be a group that is substituted with $-C(O)R^{13}$ or $-SO_2R^{13}$. In Scheme 1, BOC-protected amino acids (12.0) are available commercially or can be made by procedures well known in the art. These amino acids can be coupled (step 1) to a commercially availble N-benzylprotected amino acid, ethyl ester using suitable coupling agents such as DCC or EDC in suitable solvents (e.g., N, N-dimethylformamide, chloroform or methylene chloride) to produce a compound of Formula 13.0. Generally, this reaction is conducted at room temperature (i.e., about 25°C). The BOC protecting group is removed (step 2) at room temperature with suitable reagents such as trifluoroacetic acid, or hydrogen chloride in chloroform or dioxane. The deprotected dipeptide is cyclized (step 3) under basic conditions to produce the compound of Formula 14.0. The compound of Formula 14.0 is then reduced (step 4) using $LiAlH_4$ in refluxing ether (diethyl ether) or THF to give the piperazine of Formula 15.0. The unsubstituted nitrogen of the piperazine of Formula 15.0 is protected (step 5) with a BOC group by procedures well known in the art to give the compound of Formula 16.0. The N-benzyl group is removed (step 6) by catalytic hydrogenation (e.g., using Pd/C and hydrogen gas under pressure of about 60 psi) to give the compound of Formula (9.0). Alternatively, compound (15.0) can be converted to the FMOC derivative (15.3) by treatment with FMOC-Cl in the presence of a base such as sodium bicarbonate in an aqueous dioxane. The FMOC derivative (15.3) can be debenzylated as described in step 6 above, to give compound (15.5). Compound (15.5) can be converted to the BOC-derivative (15.7) by procedures known in the art. Compound (15.7) can be converted to compound (4.0) by heating in a suitable hydroxyl solvent such as methanol.

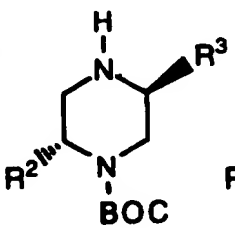
Those skilled in the art will appreciate that the compound of Formula 9.0 can exist as the following enantiomers



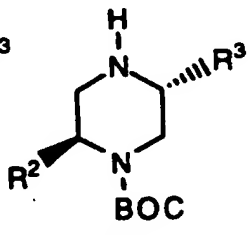
(9.1)



(9.2)

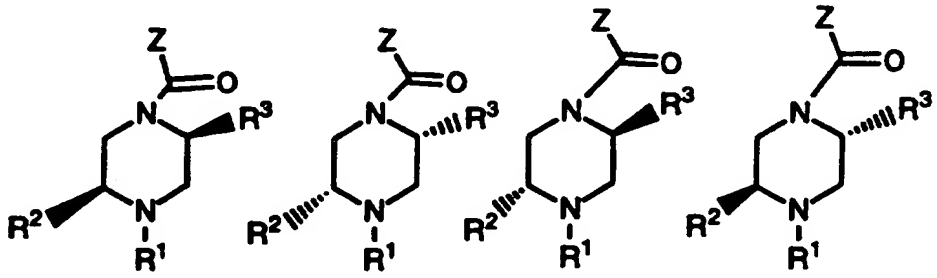


(9.1a)



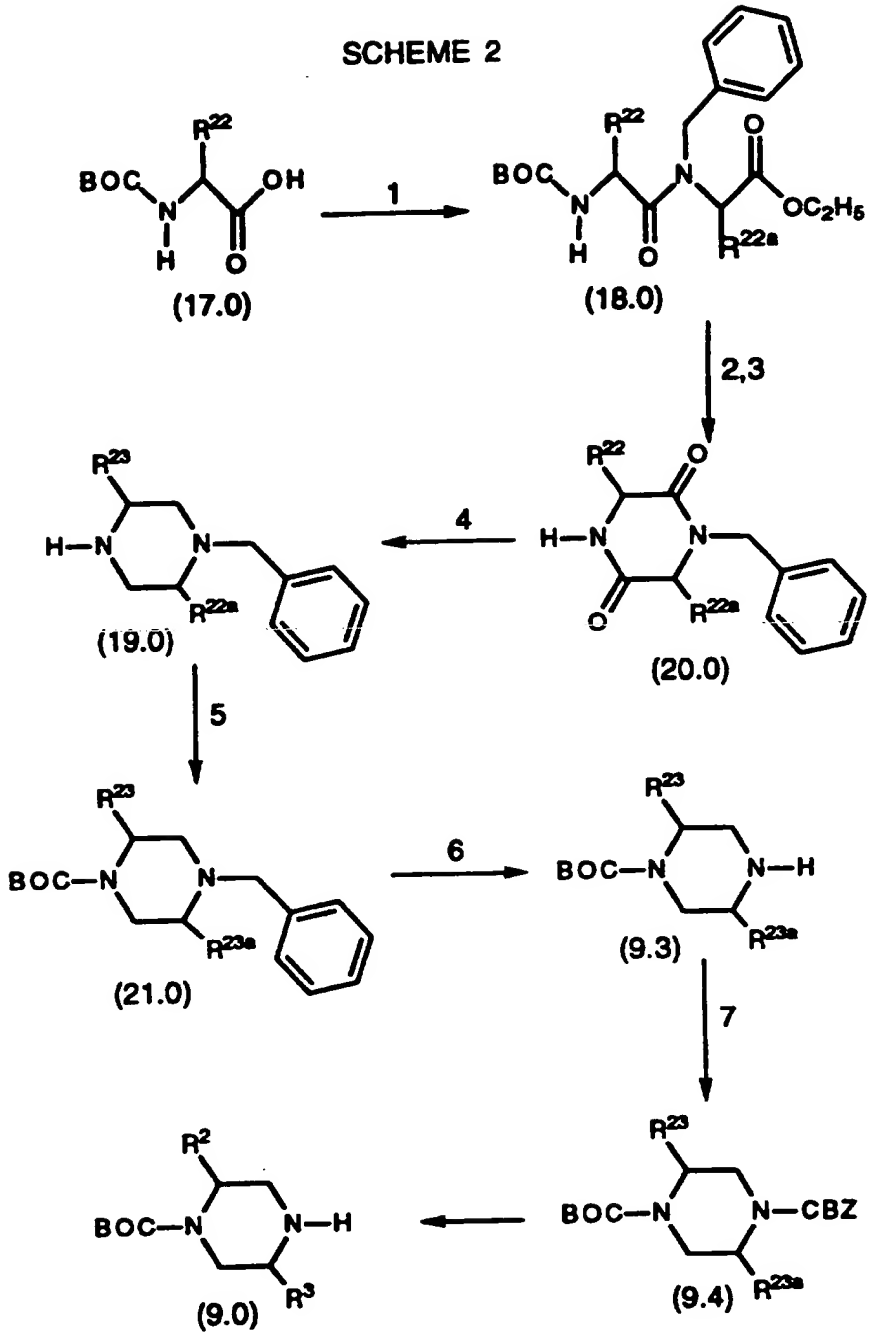
(9.2a)

These piperazinyl isomers yield th desired isomers of compound (1.0) shown below:



(1.1) (1.2) (1.1a) (1.2a)

SCHEME 2



Compounds (9.0), wherein R^2 and R^3 independently represent alkyl, alkenyl or alkynyl substituted with (a), (c), (d) or (g) groups wherein R^8 or R^9 are substituted with $-C(O)R^{13}$ or $-S(O)_2R^{13}$ are made according to the process of Scheme 2. Compounds (9.0), wherein R^2 and R^3 independently represent represent $-C(O)NR^8R^9$ or $-C(O)OR^8$, or wherein R^2 and R^3 independently represent alkyl, alkenyl or alkynyl substituted with its groups ( ), (f), or (h)-(p) are also made according to th process of Scheme 2. Compounds (17.0) and (18.0),

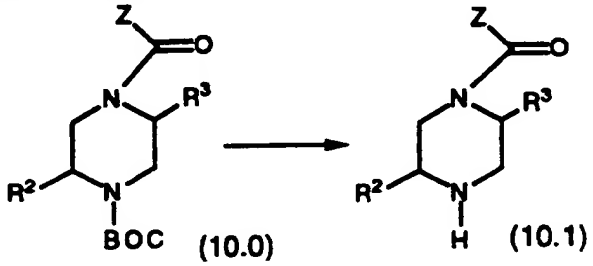
wherein R^{22} and R^{22a} independently represent alkyl, alk nyl or alkynyl group containing ither a -OH group, a -COOH or its corresponding ester, are available commercially or can be made by procedures known in the art. In Scheme 2, the compound (17.0) is reacted according to the procedures described for Scheme 1 (steps 1 to 4) to produce a compound (19.0) wherein R^{23} and R^{23a} independently represent a hydroxy substituted alkyl, alkenyl or alkynyl group. The compound (19.0) is then protected with a BOC group and then debenzylated according to the procedures in Scheme 1 (Steps 5 and 6) to produce a compound (9.3). The unsubstituted nitrogen of compound (9.3) is protected (step 7) with a CBZ group by procedures known in the art to produce the compound (9.4). The groups R^{23} and R^{23a} on compound (9.4) can be converted to R^2 and R^3, respectively, followed by deprotection of compound (9.4) by catalytic hydrogenation, i.e. palladium/carbon and hydrogen in a suitable solvent such as methanol, to give compound (9.0).

When R^{23} and R^{23a} of compound (9.4) is $-CH_2OH$, the hydroxy group can be oxidized to produce the corresponding carboxyl group-(COOH). This carboxyl group can them be esterified to produce compounds wherein R^2 is $-C(O)OR^8$, or the carboxyl group can be converted to amides to produce compounds wherein R^2 or R^3 are $-C(O)NR^8R^9$ by procedures well known in the art.

To produce compounds (9.0) in Scheme 2 wherein R^2 and/or R^3 is a substituent other than $-C(O)OR^8$ or $-C(O)NR^8R^9$, the hydroxy group on R^{23} or R^{23a} in compound (9.4) can be converted to a leaving group, such as chloro, mesyloxy or tosyloxy, by techniques well known in the art. Then the leaving group can be displaced by various nucleophiles such as organometallics (to produce R^2 and/or R^3 with an (a) substituent), thiols (to produce R^2 and/or R^3 with a (d) substituent), sulfenyls (to produce R^2 and/or R^3 with an (e) substituent), sulfinyls (to produce R^2 and/or R^3 with an (f) or (m) substituent), amines (to produce R^2 and/or R^3 with a (g) substituent), and alcohols (to produce R^2 and/or R^3 with a (c) substituent). The hydroxy group on R^{23} and/or R^{23a} in compound (9.4) can also be acylated (to produce R^2 and/or R^3 with a (j) or (k) substituent) or alkylated (to produce R^2 and/or R^3 with a (c) substituent). When R^{23} and/or R^{23a} in compound (9.4) is alkyl having more than one carbon atom, or alkenyl or alkynyl, the hydroxy group can be oxidized, as discussed above, to produce the corresponding carboxyl group (i.e., substituent (o) wherein R^8 is H). This carboxyl group can be esterified to produce compounds wherein substituent (o) is $-C(O)OR^8$ wherein R^8 is other than H, or converted to amides to produce to produce R^2 and/or R^3 with an (l) substituent by procedures well known in the art. When th leaving group is displaced by an amine (e.g., $-NR^8R^9$), the amine can

then be converted to R^2 and/or R^3 substituent groups (h), (i) or (n) by reacting th amine with an acyl halide (to produce R^2 and/or R^3 with an (h) substituent), a carbamyl halide (to produce R^2 and/or R^3 with an (i) substituent) or a sulfonyl halide (to produce R^2 and/or R^3 with an (n) substituent) by procedures well known in the art, which following deprotection, give compound (9.0).

The compound of Formula 10.0 can be deprotected (i.e., the BOC group removed) by treatment with an acid (e.g. trifluoroacetic acid, or HCl-dioxane) to produce the compound (10.1).



A2. Preparation of Piperazinyl Compounds.

Compound (10.1) can be converted to the desired piperazinyl compound (1.0), wherein X^1 is N, by acylation, acylation and deprotection or reductive alkylation, optionally with deprotection.

Acylation of the compound (10.1) can be carried out by reacting it with a compound having a carboxylic acid moiety contained in or part of the desired R^1 group, with a coupling agent, such as a carbodiimide such as dicyclohexylcarbodiimide(DCC) or DEC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide). The acylation reaction can be carried out in a suitable organic solvent such as DMF, THF or methylene chloride at a temperature of about -10° to about 100°C, preferably at about 0° to about 50°C, and most preferably about room temperature. When the coupling reagent is DCC or DEC, the reaction is preferably conducted in the presence of HOBT.

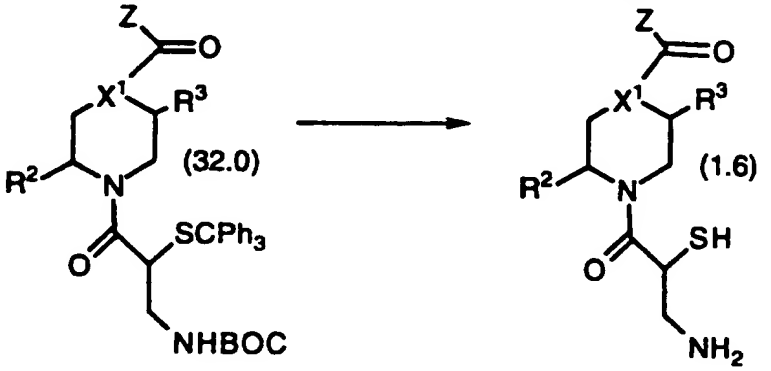
Compounds (1.0), wherein R^1 is a substituent (a-e, g, i-q, u-cc, ee, gg-ll, nn-ooo) can be made by reacting a compound (10.1) with R^1-L, wherein R^1 contains the -C(O)- group and L is a leaving group such as Cl, Br, I, or a carboxylate (an anhydride). The reaction is carried out in the presence of a base, preferably a tertiary amine such as triethylamine or N-methyl morpholine.

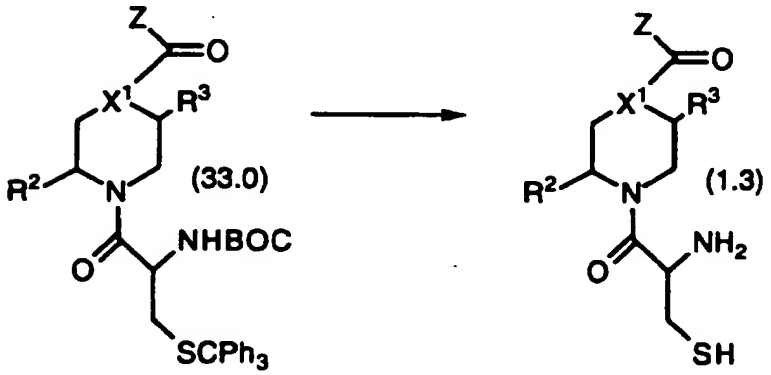
Specifically, compounds (1.0) wherein R^1 is a substituent (u) to (y) can be made by reacting a compound of Formula (10.1) or (30.0) with a pyridyl chloroformate or piperidyl chloroformate; or, alternatively, reacting a compound (10.1) or (30.0) with xcess phosgene and reacting the chloroformate thus produced with a hydroxypyridyl N-oxide or hydroxypiperidine derivative. The

reaction is carried out in a suitable solv nt, such as dichloromethane, in the presence of a tertiary amine, such as pyridine, by techniques well known in the art.

Alternatively, compounds (1.0), wherein R^1 is a substituent (m) to (q) can be made by reacting a compound (10.1) with a pyridyl isocyanate, pyridyl N-oxide isocyanate or piperidyl isocyanate corresponding to the pyridyl, pyridyl N-oxide or piperidyl moiety, respectively, of the substituent groups (m) to (q). The reaction is carried out in a suitable solvent such as DMF, THF or chloroform using techniques well known in the art. Alternatively, these ureas can be prepared by reacting a compound (10.1) with phosgene to form a chloroformate intermediate (R^1 is -C(O)Cl). This chloroformate is generally not isolated, and is reacted with pyridyl amine, pyridyl N-oxide amine or piperidyl amine corresponding to the pyridyl, pyridyl N-oxide or piperidyl moiety, respectively, of the substituent groups (m) to (q) by techniques well known in the art.

When compounds of Formulas 10.1 (X^1 is N) or 30.0 (X^1 is CH) are acylated to make the compounds (1.0) wherein R^1 is substituents (g) or (e), the protected compounds of Formulas 32.0 and 33.0, respectively are formed.

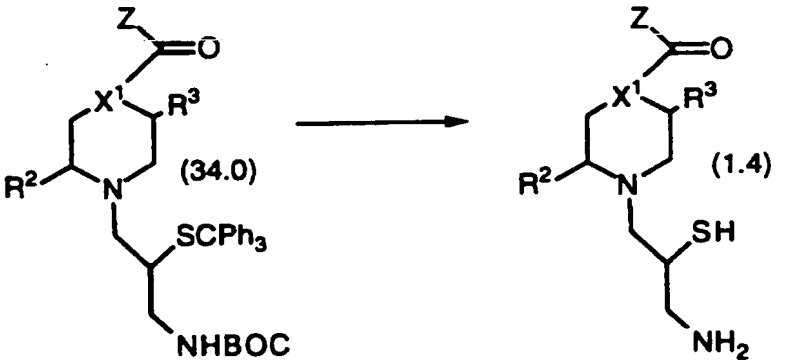


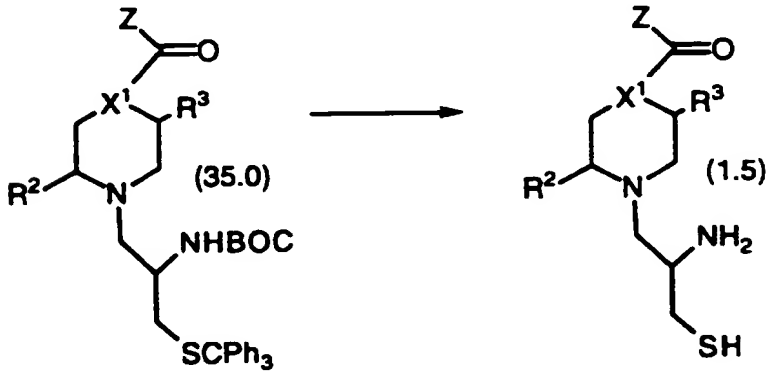


Protected compounds (32.0) and (33.0) can be deprotected by using trifluoroacetic acid and triethylsilane to yield compounds (1.6) and (1.3), respectively, which are isolated as the hydrochloride salts.

Reductive alkylation (i.e. reductive amination) of compound (10.1) can be accomplished by reacting compound (10.1) with an aldehyde in DMF with a dehydrating agent such as molecular sieves at room temperature (about 25°C). This reaction is followed by reduction of the intermediate imine with a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride. The reduction is usually carried out at room temperature in a suitable solvent such as DMF.

When compounds of Formulas 10.1 (X^1 is N) or 30.0 (X^1 is CH) are reductively alkylated to make the compounds (1.0) wherein R^1 is substituents (h) or (f) , the protected compounds (34.0) and (35.0), respectively are formed.





These protected compounds can be deprotected by using trifluoroacetic acid and triethylsilane to give, respectively, compounds (1.4) and (1.5) which are isolated as the hydrochloride salts.

Compounds of Formula (1.0) wherein R^1 is a substitutent (u) to (y) can be made by reacting a compound R^1-Cl, wherein R^1 is a substituent (u) to (y), with a compound of Formula 10.1 or 30.0, in dichloromethane with a t rtiary amine

bas . The reaction is conducted at about 0° to about 60°C for about 1 to about 70 hours.

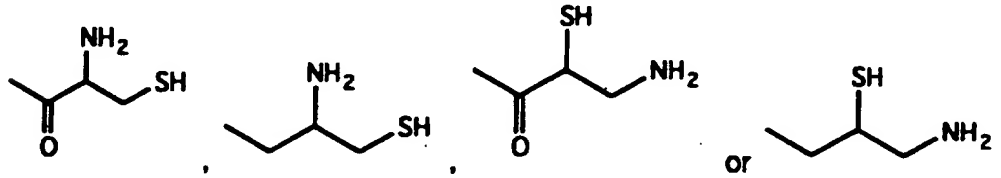
Certain compounds of Formula (1.0) can be converted to oth r compounds of the F rmula (1.0) using standard reaction conditions. For example, compounds of the formula (1.0) wherein R^2 and/or R^3 is $-CO_2H$, (i.e., $-C(O)OR^8$ and R^8 is H), can be prepared by ozonolysis of a compound (1.0) wherein R^2 and/or R^3 is $CH_2=CH-$, followed by oxidation of the resulting aldehyde to give other desired compounds (1.0).

Compounds (1.0) wherein R^2 and/or R^3 is $-C(O)OR^8$, where R^8 is other than H, can be prepared from compound (1.0) wherein R^2 and/or R^3 is $-CO_2H$ by treating with $SOCl_2$ or oxalyl chloride, then with an alcohol of the formula R^8OH, wherein R^8 is as defined above. Similarly, compounds of formula (1.0) wherein R^2 and/or R^3 is $-C(O)NR^8R^9$ can be prepared from a compound (1.0) wherein R^2 and/or R^3 is $-CO_2H$ via essentially the same method but substituting an amine of the formula R^8R^9NH for the alcohol R^8OH. Alternatively, compounds of Formula (1.0) wherein R^2 and/or R^3 is $-C(O)NR^8R^9$ can be prepared by reacting a compound (1.0) wherein R^2 and/or R^3 is $-CO_2H$ with an amine R^8R^9NH in the presence of a coupling agent, such as DCC or DEC.

In an analogous manner, compounds (1.0) wherein R^2 and/or R^3 is alkyl substituted by a group of the formula $-C(O)OR^8$ or $-C(O)NR^8R^9$ can be prepared via substantially the same procedures as described above to form compounds wherein R^2 and/or R^3 is $-CO_2H$, $-C(O)OR^8$ or $-C(O)NR^8R^9$, by replacing the compound (1.0) wherein R^2 and/or R^3 is $CH_2=CH-$ with an appropriate alkenyl group, (i.e., a group of the formula $-(CH_2)_p-CH=CH_2$, wherein p is 1, 2, 3, 4, etc.).

Compounds (1.0) wherein R^2 and/or R^3 contains a substituent of formula $-S(O)_tR^8$, wherein t = 1 or 2, can be prepared by oxidation of an analogous compound of the formula (1.0) wherein R^2 and/or R^3 contains a substituent of formula $-S(O)_tR^8$, wherein t = 0, using a suitable oxiding agent, such as a peracid, preferably MCPBA.

One skilled in the art will recognize that the above transformations may, in certain instances, such as where R^1 is a group of the formula

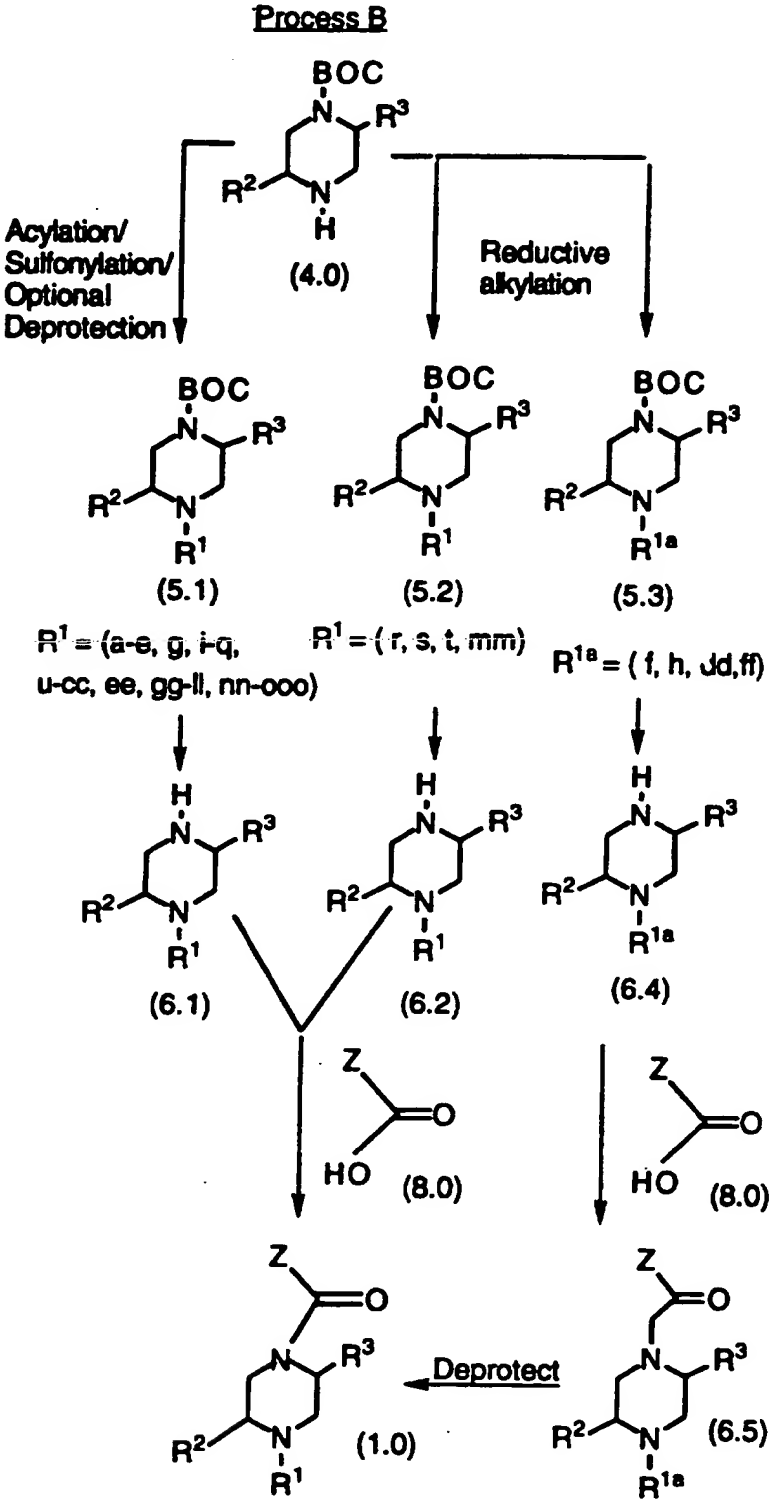


require that the oxidation be carried out prior to introduction of the R^1 group to formula (1.0).

Compounds (1.0) where the -Z group contains an N-O moiety, can be prepared by treatm nt of the carboxylic acid (8.0) containing a nitrog n atom (N) in the aromatic ring, with an oxidizing reagent, such as m-chloroperoxybenzoic acid or hydrogen peroxide and acetic acid. The subsequent carboxylic acid (8.0) containing the N-O moiety can be treated as described herein to give desired compound (1.0).

B. Process B for Preparing Piperazinyl Compounds

In alternative Process B, the piperazinyl compounds (1.0) of the present invention can be prepared according to the following Process B.

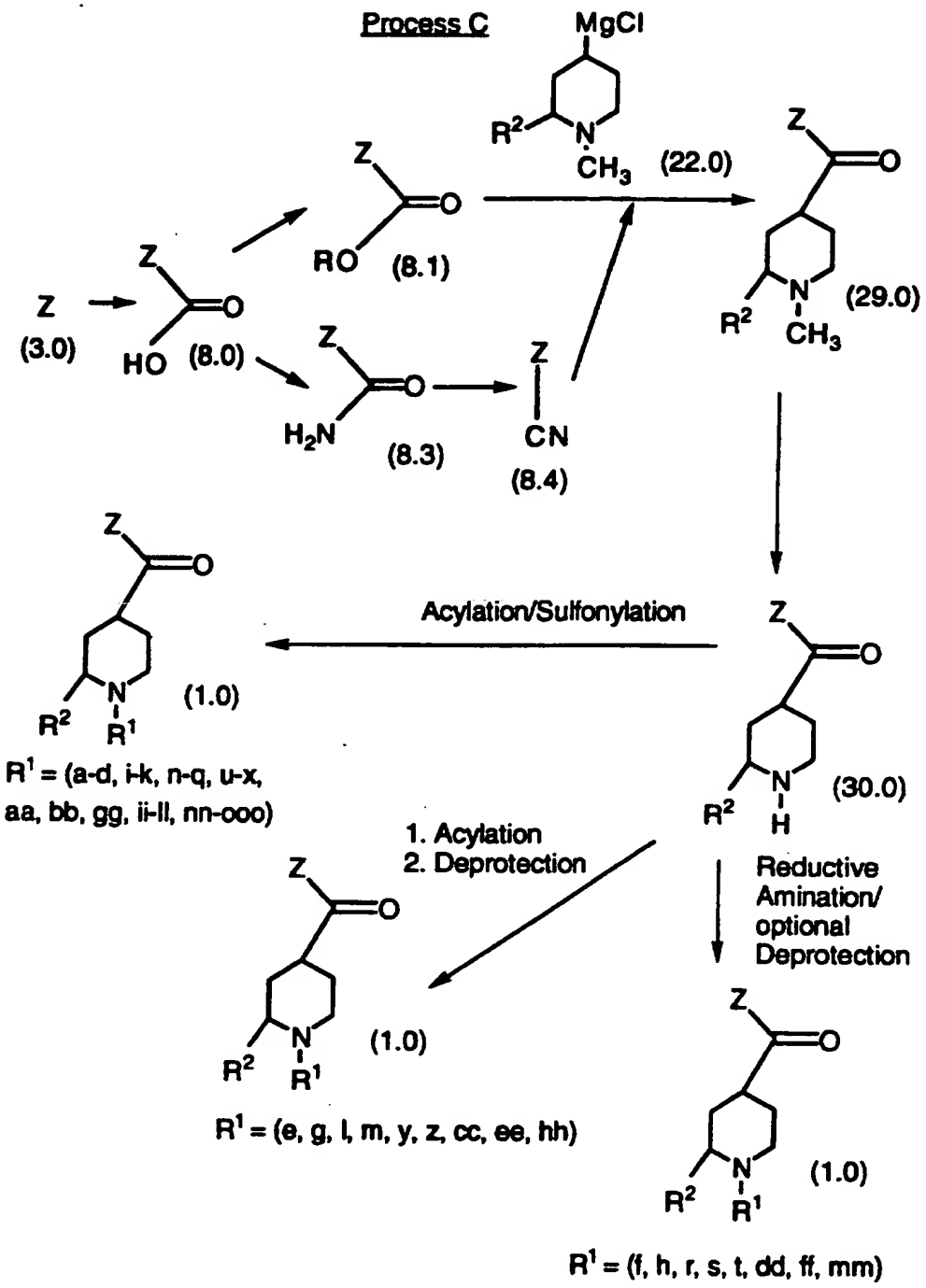


wherein Z, BOC, R^1= (a-ooo), R^2 and R^3 are as defined herein. It is also understood that groups R^1=(e, g, cc and ee) in compound (5.1) and groups

R^1=(r, s, t, mm) in compound 5.2 and R^1=(f, h, dd and ff) in compound (5.3) are either N-protected as the BOC derivative r both N-protected as the BOC derivative and S-protected as the trityl (triphenylmethyl) derivative.

Process B, compound (4.0) can be either acylated or reductively alkylated (ie. reductively aminated) as described hereinbefore, to incorporate the R^1 group to give compounds (5.1), (5.2) and (5.3) respectively. Compounds (5.1), (5.2) and (5.3) can be deprotected with any suitable acid, such as trifluoracetic acid (TFA) or dioxane saturated with HCl gas, in a suitable solvent, such as methylene chloride (CH_2Cl_2) or dioxane to remove the BOC protecting group and yield compounds (6.1), (6.2) and (6.4), respectively. Reaction of compounds (6.1), (6.2) and (6.4) with carboxylic acid (8.0) under conditions and with reagents as described herein, gives the desired piperazinyl compounds (1.0) and (6.5).Compound (6.5) is deprotected as described herein to give compound (1.0).

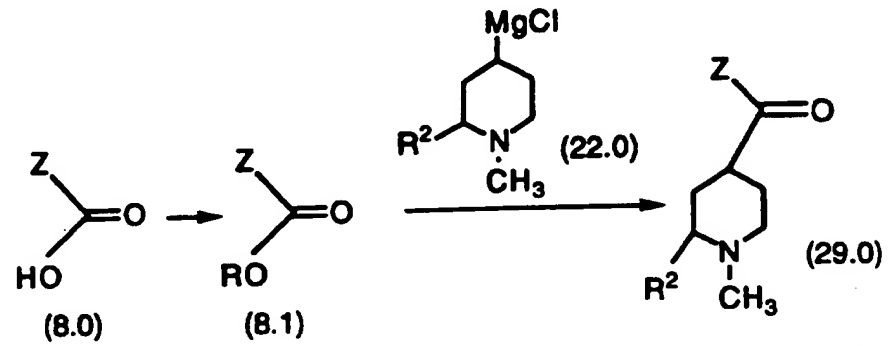
C. Piperidinyl Compounds and Starting Materials. The piperidinyl compounds of the present invention and starting materials thereof, can be prepared according to the following overall Process C.



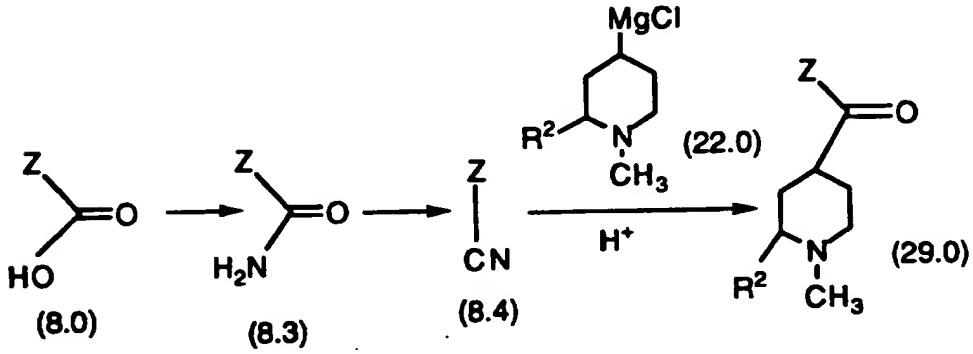
wherein Z, R, R^1=(a-ooo) and R^2 are as defined herein.

C1. Preparation of Piperidinyl Starting Materials.

The preparation of aromatic compounds (3.0) and their corr sponding carboxylic acids (8.0) has been described in the section A1, for the preparation of the piperizinyl starting materials.

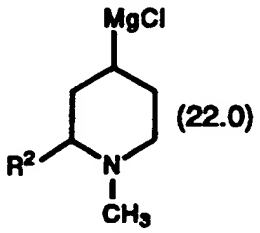


The carboxylic acids (8.0) can be converted to esters (8.1) by reacting the carboxylic acid with an alcohol such as methanol, in the presence of an acid such as sulfuric or hydrochloric acid to give ester (8.1). Ester (8.1) can be converted to the piperidyl ketone (29.0) by reaction of ester (8.1) with an organometallic reagent (22.0), such as as a Grignard reagent or an organolithium reagent.



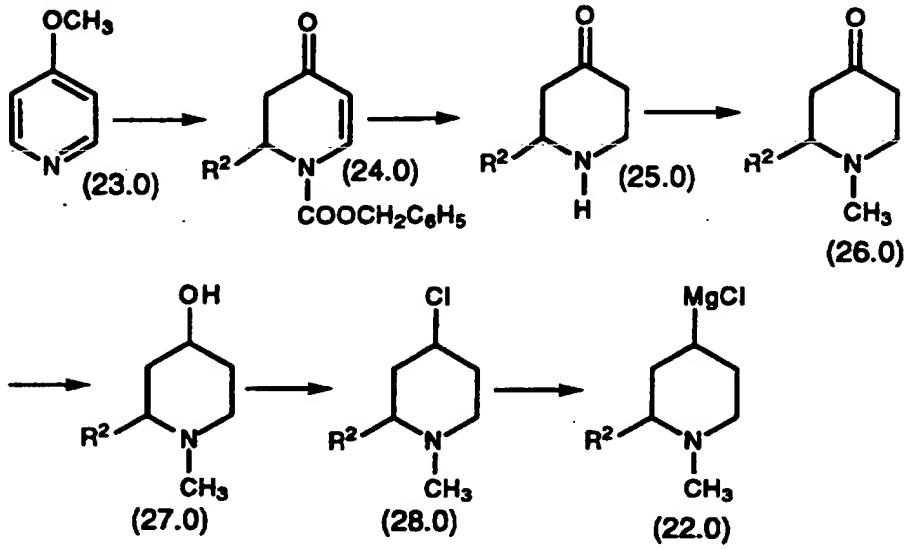
In an alternative reaction, the carboxylic acids (8.0) can be converted into amides (8.3) by treatment with ammonia and a coupling agent such as DCC or DEC. The amide (8.3) can then be dehydrated to nitrile (8.4) by treatment with a reagent such as phosphorous pentachloride (P_2Cl_5), thionyl chloride ($SOCl_2$) or acetic anhydride by methods well known to those skilled in the art, as taught in Ian Harrison and Shuyen Harrison, Compendium of Organic Synthetic Methods, John Wiley and Sons, New York, (1971) and Volume 2, (1974). The nitrile (8.4) can be converted to ketone (29.0) by treatment with an organometallic reagent, such a Grignard reagent or an organolithium reagent, followed by hydrolysis with acid to give protonated piperidyl keton (29.0).

Compounds (1.0) wherein X^1 is CH, and R^2 is alkyl, alk nyl or alkynyl, or R^2 is alkyl, alkenyl or alkynyl substituted with substituents (a), (b), (c), (d), or (g) with the exception that substituents R^8 or R^9 cannot have a halogen, -OH, $-C(O)R^{13}$ or $-SO_2R^{13}$ substituent, can be made from compounds of the Formula 22.0:



(22.0)

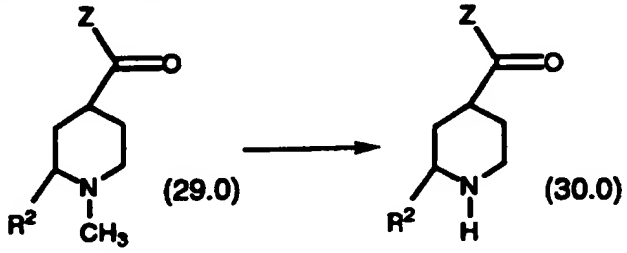
Compound (22.0) can be made according to the process:



The substituted piperidines (22.0) may be prepared, as racemic mixtures, by essentially the same methods as described in D.L. Comins and J.D. Brown, Tetrahedron Letters, vol. 27 No. 38, pgs. 4549 -4552, 1986. Thus, 4-methoxypyridine (23.0) may be converted using a variety of alkyl Grignard reagents (wherein R^2 is as illustrated below) and benzylchloroformate to the desired unsaturated ketopiperidines (24.0). Removal of the benzylcarbamoyl group with concomitant reduction of the double bond by catalytic hydrogenation yields the substituted ketopiperidines (25.0). Alternatively, the benzylcarbamoyl group can be removed with either base or acid followed by metal hydride reduction of the double bond to produce compound (25.0). Alkylation of the compound (25.0) with a suitable alkyl iodide such as methyl iodide in the presence of sodium hydride gives the n-alkylketopiperidines (26.0). Reduction of compound (26.0) with sodium borohydride affords the hydroxypiperidine (27.0). Compound (27.0) is reacted with a suitable chlorinating agent such as thionyl

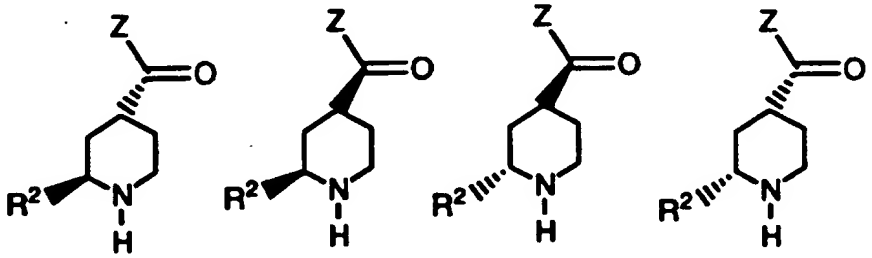
chloride to afford th 4-chloropiperidin (28.0) which may in turn be converted by reaction with magnesium into compound (22.0).

Compound (22.0) is reacted with the compound (8.1 r 8.4), described above, in a suitable solvent such as diethyl ether or THF. The reaction is conducted at room temperature (about 25°C) to about 50°C. This reaction is then followed by aqueous acid hydrolysis to yield ketones (29.0):



The N-methyl group on the piperidine ring can be converted to a carboethoxy group (-$COOC_2H_5$) or a carbochloroethoxy group (-$COOCHClCH_3$) by reaction with excess ethyl chloroformate or 1-chloroethylchloroformate in dry toluene or dichloroethane containing triethylamine at a temperature of about 80°C. This procedure is similar to that described in U.S. Patents 4,282,233 and 4,335,036. The carboethoxy group can be removed by either acid or base hydrolysis to give the compound (30.0). The carbochloroethoxy group can be removed by heating in methanol to give (30.0).

Compounds (30.0) are prepared as diasteromeric mixtures. Preferably, the diasteriomers are separated into single isomers by classical resolution methods or by chiral HPLC to yield:



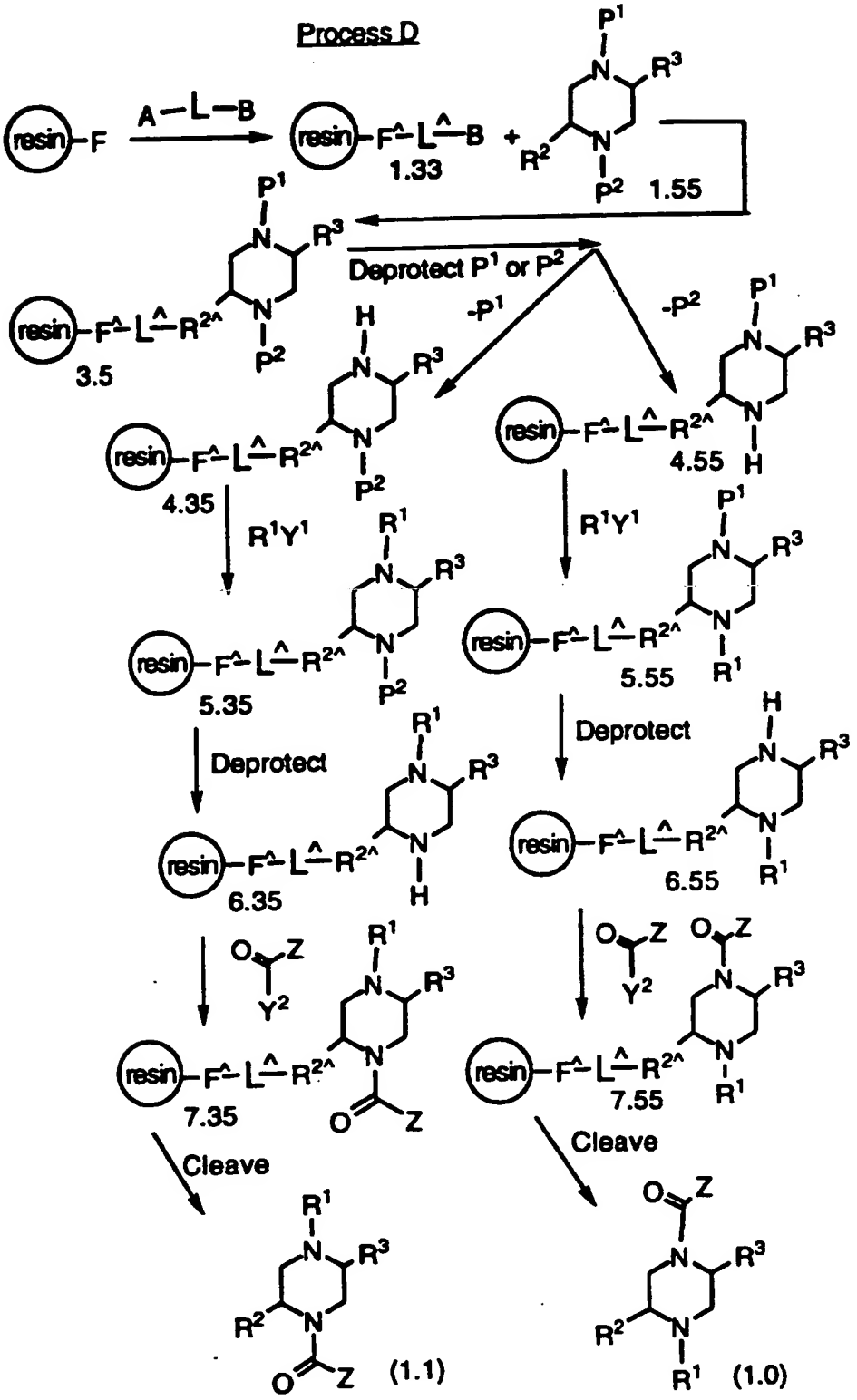
Compound (30.1), (30.2), (30.3) and (30.4) can be converted to the compound (1.0), wherein X^1 in (1.0) is CH, by acylation or reductive alkylation.

C2. Preparation of Piperidinyl Compounds.

The piperidinyl compounds (1.0) wher in X^1 is CH, can be pr pared from the piperidinyl ketone (30.0), by using the acylation, acylation and deprotection or reductive alkylation/optional deprotection procedures described for Process A or B.

D. Process D for Preparing Piperazinyl Compounds

In an alternative embodiment, an encoded combinatorial library of compounds compounds (1.0) wherein X^1 is N and R^2 has a suitable functional group, can be prepared using combinatorial methods on a solid phase as described in WO94/08051, April 1994, whose preparative teachings are incorporated herein by reference and according to the following Process D.



In Process D, a resin, e.g. (resin)-F, is selected which contains a functional group, (-F), which can couple, r form a covalent bond with a suitable linker (A-L-B).

Suitable functional (-F) groups include primary and secondary amines, hydroxy, thiol, carboxylic acid, halide and th like. The linker can be any compound having (a) a complementary functional "A-" group (e.g. amine, hydroxy, thiol, carboxylic acid, halide and the like) which can couple, or form a covalent bond with (resin)-F, and (b) a functional "-B" group (e.g. hydroxy, primary or secondary amine, thiol, carboxylic acid and the like) capable of forming a covalent bond with a suitable functional group in either R^2 or R^3 of a substituted, N-protected piperazine (1.5), such as an amide or carboxylic acid group in R^2 or R^3, and (c) any organic or inorganic moiety L having bound to it functional groups A and B. Representative linkers include, but are not limited to 4-(bromomethyl)-3-nitrobenzoic acid and 4-(hydroxymethyl)phenol. The linker can be coupled to (resin)-F in a suitable solvent (e.g. DCM or methanol), optionally in the presence of a catalyst suitable for the particular coupling reaction.

Reagents and reaction conditions for protecting and deprotecting compounds is well known, as described, for example, in T.W. Greene and P. Wuts, Protective Groups in Organic Synthesis, 2nd Ed., Wiley Interscience, N.Y. 1991, 473 pages. In addition to having a suitable functional group in either its R^2 or R^3 group, piperazine 1.55 has protecting groups, P^1 and P^2 orthogonal to each other and to the linker. Suitable protecting groups include but are not limited to BOC, FMOC, CBZ, allyloxycarbonyl (ALLOC), benzyl, o-nitrophenyl and the like. The resin/linker 1 can be coupled to N-protected piperazine 1.55 in the presence of a suitable solvent, optionally in the presence of a catalyst suitable for the particular coupling reaction to give the coupled piperazine 3.5.

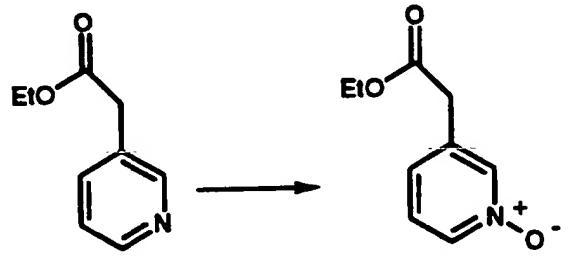
One of protecting groups P^1 or P^2 can be removed by treatment with a suitable deprotecting agent or process, including but not limited to TFA, piperidine, hydrogenolysis, photolysis and the like to give partially deprotected piperazine 4.35 or 4.55. Piperazine 4.35 or 4.55 can then be reacted with compound R^1Y^1 wherein R^1 is as defined before and Y^1 is a suitable leaving group, in a suitable solvent, optionally in the presence of a catalyst suitable for the particular reaction, to give partially protected piperazine 5.35 and 5.55. Compound 5.35 and 5.55 can be deprotected as described above to give deprotected compound 6.35 or 6.55. Compound 6.35 and 6.55 can be reacted with carbonyl compound $Z(CO)Y^2$ wherein Z is defined before and Y^2 is a suitable leaving group to give compound 7.35 or 7.55. The "^" in moieties such as R^{2}^, F^ and L^ indicate that at least one functional group in that moiety is covalently bonded to another functional group.

Compound 1.0 can be prepared by cl aving th coupling between th linker and $R^{2^{\wedge}}$ using a suitable reagent or process suitable for the particular bond coupling,.e.g. photolysis, acidolysis, hydrolysis and the like.

Compounds of the present invention and preparative starting mat rials therof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art, such as by the methods described in WO95/10516.

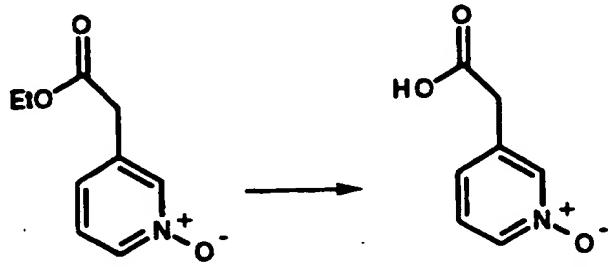
PREPARATIVE EXAMPLE 1

A. ETHYL 3-PYRIDYLACETIC ACID 1-N-OXIDE



Ethyl 3-pyridylacetic acid (10grams) (60.6 mmoles) is dissolved in dry CH_2Cl_2 (120ml) and the solution is stirred at -18°C for 30 minutes. MCPBA (31.34 grams) (181.6 mmoles) is added and the mixture is stirred at -18°C for 1 hour and then at 25°C for 87 hours. The reaction mixture is diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate and then water. The CH_2Cl_2 is then dried (magnesium sulphate), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 3% (10% concentrated ammonium hydroxide in methanol)-CH_2Cl_2 as the eluant to give the title compound (Yield: 8.45 grams, 77%, MH^+ 182).

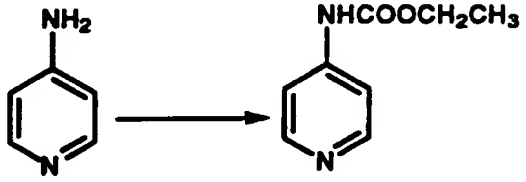
B. 3-PYRIDYLACETIC ACID 1-N-OXIDE



Ethyl 3-Pyridylacetic acid 1-N-oxide (0.2747 grams) (1.5 mmoles) is dissolved in ethanol (200 proof) (1.22 ml.) and a 1M solution of LiOH in water (3.64 ml.) (3.0 mmoles) is added and the mixture is stirred at 25°C for 4 hours. 1N HCl (4.28 ml.) is added and the mixture is pumped down to dryness on a rotary evaporator to give the title compound (Yield: 0.2931 grams, 100%).

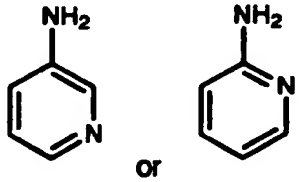
PREPARATIVE EXAMPLE 2

4-ETHOXYCARBONYLAMINOPYRIDINE



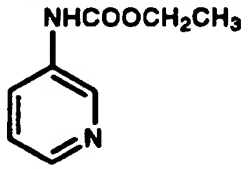
4-Aminopyridine (17.34 grams) (184.3) is dissolved in dry pyridine (217 ml.) and cooled to 0°C over 30 minutes. Ethyl chloroformate (17.2 ml.) (180.7 mmoles) is added and the solution is stirred at 0°C for 1 hour and then at 25°C for 40 hours. The mixture is diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and water. The CH_2Cl_2 is dried ($MgSO_4$), filtered and evaporated to dryness. The residue is chromatographed on silica gel using 2%(10% saturated NH_4OH in MeOH)-CH_2Cl_2 to give the title compound (Yield: 10 grams, 33%, M^+ 166).

By using essentially the same procedure, with the exception that

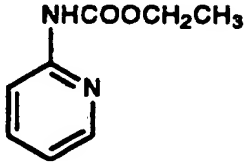


or

is used instead of 4-aminopyridine, the compound



Amorphous solid, MH^+ 167



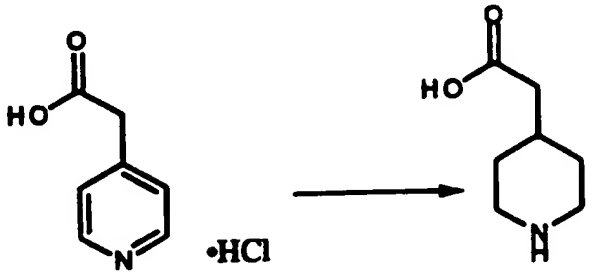
Amorphous solid, MH^+ 167

or

is obtained, respectively.

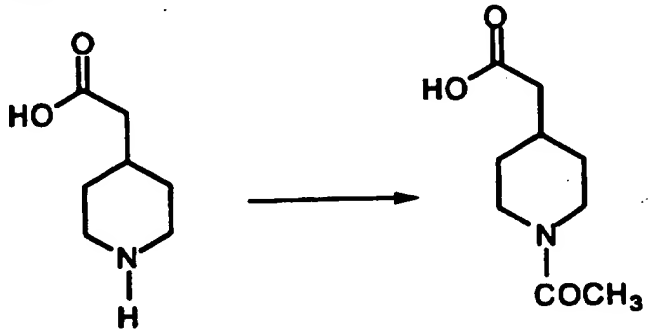
PREPARATIVE EXAMPLE 3

A. PIPERIDINE-4-ACETIC ACID



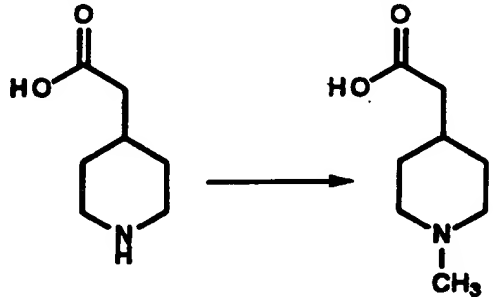
4-Pyridylacetic acid hydrochloride (7 grams) (40.4 mmoles) is hydrogenated in water (100 ml) using 10% Pd-C at 40 psi at 25°C for 24 hours. The catalyst is filtered off and washed with water. The aqueous solution is shaken with BioRad AG1X8 resin (OH^- form) (23 ml bed) and after 5 minutes the resin is filtered off and washed with water. The aqueous solution is evaporated to give the title compound (Yield: 5.2 grams, 90%, MH^+ 144).

B. 1-N-ACETYL-4-PIPERIDINYLACETIC ACID



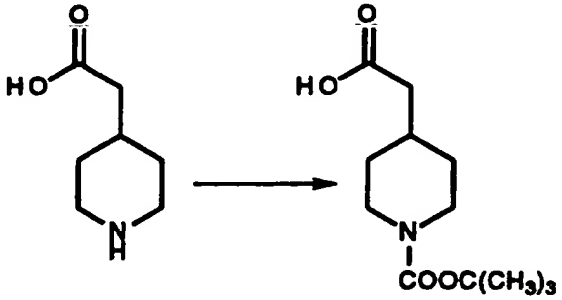
4-Piperidinylacetic acid (5 grams) (35.0 mmoles) is reacted with acetic anhydride (10.7 grams) (105.0 mmoles) in MeOH (100 ml.) and the mixture is stirred at 25°C for 24 hours. The mixture is evaporated to dryness and the residue is azeotroped with toluene to give the title compound (Yield: 6.4 grams, 99%, MH^+ 185).

C. 1-N-METHYL-4-PIPERIDINYLACETIC ACID



4-Piperidinylacetic acid (4 grams) (28.0 mmoles) from Preparative Example 3A is dissolved in water (50 ml) and 37% formalin (2.72 ml) (33.6 mmoles) is added. The mixture is hydrogenated over 10% Pd-C at 55psi at 25°C for 68 hours. The catalyst is filtered off and washed with water. The combined filtrates are evaporated to dryness to give the title compound (MH^+158).

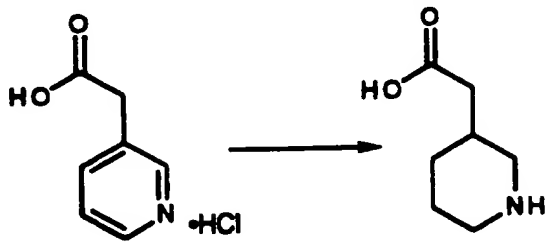
D. 1-N-tert-BUTOXYCARBONYLPIPERIDINYL-4-ACETIC ACID



4-Piperidinylacetic acid (41.24 grams) (288.4 mmoles) from Preparative Example 3A is dissolved in THF-water (1:1) (400 ml) and di-tert-butyldicarbonate (69.14 grams) (317.3 mmoles) and NaOH (11.52 grams) (288.4 mmoles) are added. The mixture is stirred at 25°C for 72 hours. The solution is then eluted through a bed of washed BioRad 50WX4 (RSO3H resin) (150 ml bed) and the resin is eluted with a 1:1 mixture of THF and water. The eluate is evaporated to dryness to give the title compound (Yield: 53.0 grams, 76%).

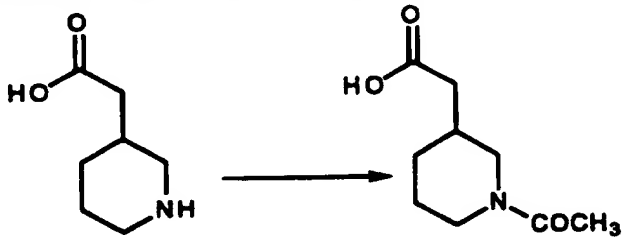
PREPARATIVE EXAMPLE 4

A. 3-PIPERIDINYLACETIC ACID



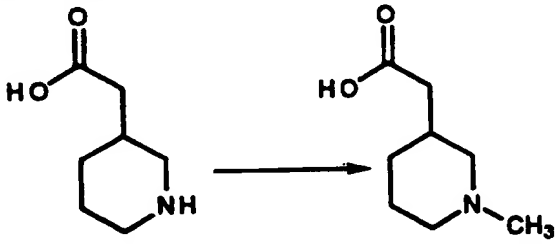
3-Pyridylacetic acid hydrochloride (13 grams) (74.9 mmoles) is hydrogenated as described in Preparative Example 3A to give a mixture of unreacted 3-pyridylacetic acid and the title compound (76:24) (8.63 grams, MH^+ 144).

B. 1-N-ACETYL-3-PIPERIDINYLACETIC ACID



The mixture of compounds from Preparative Example 4A (8.56 grams) are reacted with acetic anhydride (8.56 grams) as described in Preparative Example 3A and the crude mixture of products is diluted in methanol (60 ml) and passed over a bed of BioRad AG50WX4 resin (RSO_3H) and the latter is eluted with methanol. The eluates are evaporated to dryness to give the title compound (Yield: 1.23 grams, MH^+ 186).

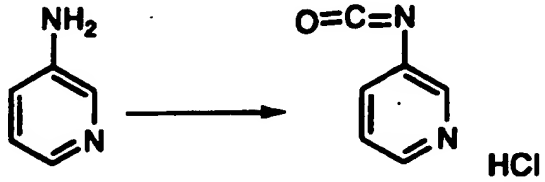
C. 1-N-METHYL-3-PIPERIDINYLACETIC ACID



The mixture of compounds from Preparative Example 4A (4 grams) and 37% formalin (2.72 ml.) are hydrogenated as described in Preparative Example 3C to give the title compound (MH^+ 158).

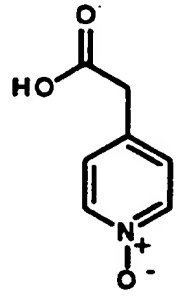
PREPARATIVE EXAMPLE 5

3-PYRIDYLISOCYANATE, HYDROCHLORIDE

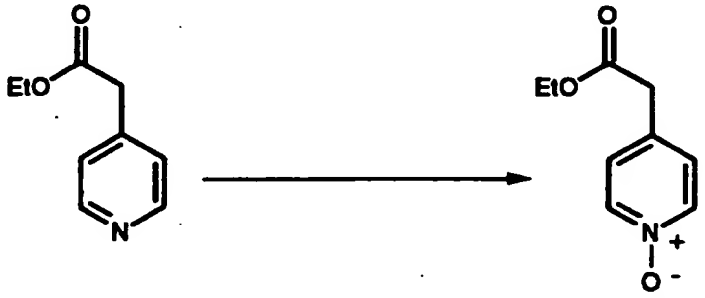


A 1.93 M solution of phosgene in toluene (20%) (584 mL) is diluted with dry CH_2Cl_2 (1 L) and the mixture is stirred at 0°C under nitrogen atmosphere. A solution of 3-aminopyridine (21.1 grams) and dry pyridine (19 mL) dissolved in dry CH_2Cl_2 (600 mL) is added dropwise to the stirred solution at 0°C over a period of 5.5 hours. The mixture is stirred at 0-25°C for an additional 48 hours. A stream of nitrogen is passed through the solution to remove most of the phosgene and the solution is then evaporated until almost all of the solvent is removed to give the title compound which is then taken up in dry pyridine (850 mL) to give a stock solution of the title compound.

PREPARATIVE EXAMPLE 6



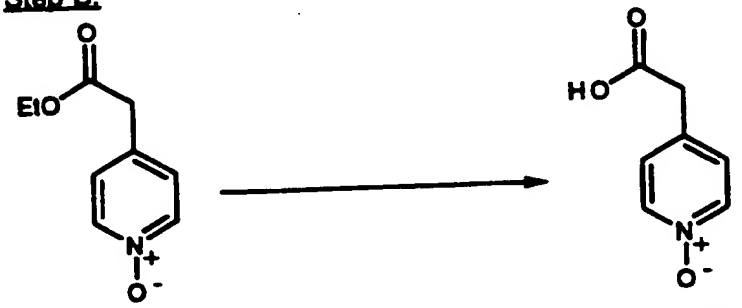
Step A:



Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C, add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmoles) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated $NaHCO_3$ (aqueous) and then water. Dry ver $MgSO_4$, concentrate *in vacuo* to a

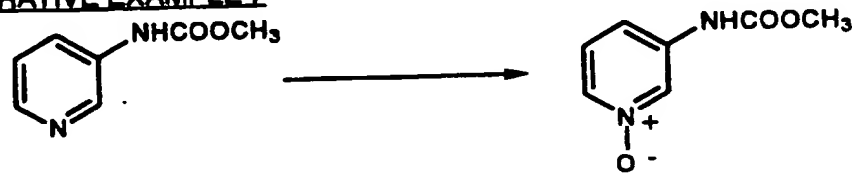
residue, and chromatograph (silica gel, 2%-5.5% (10% NH_4OH in MeOH)/CH_2Cl_2)to give 8.12 g of the product compound (Et represents -C_2H_5 in the formula). Mass Spec.: MH^+ = 182.15

Step B:



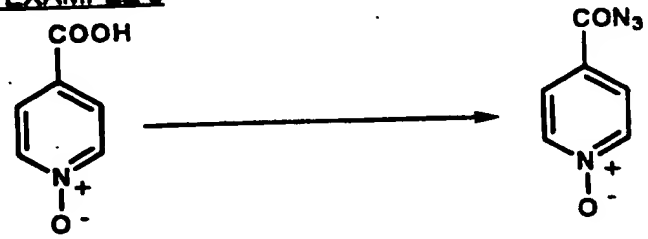
Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of ethanol and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to pH = 2.37 and concentrate *in vacuo* to a residue. Add 200 mL of dry ethanol, filter through Celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give 2.43 g of the title compound.

PREPARATIVE EXAMPLE 7



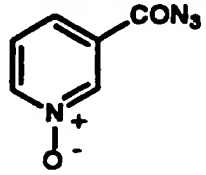
Combine 10 g (65.7 mmol) of 3-methoxycarbonylaminopyridine and 150 mL of CH_2Cl_2, cool to 0°C and slowly add (dropwise) a solution of 13.61 g (78.84 mmol) of MCPBA in 120 mL of CH_2Cl_2 at 0°C over a period of 1 hour. Stir the mixture at 25°C for 5 days, then wash with saturated $NaHCO_3$ (aqueous), then water and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% (10% NH_4OH in MeOH)/CH_2Cl_2) to give the product compound. Mass Spec.: MH^+ = 169

PREPARATIVE EXAMPLE 8



Combine 5 g (36.0 mmol) of isonicotinic acid 1-N-oxide and 150 mL of anhydrous DMF, add 5.5 mL (39.6 mmol) f triethylamine and stir at 0°C for 0.5 hours. Slowly add (dropwise) 8.5 mL (39.6 mmol) of diphenyl-phosphoryl azide at 0°C over 10 minutes, stir at 0°C for 1 hour and then at 25°C for 24 hours (as generally described in Pavia, *et al.*, Journal of Medicinal Chemistry, 33, 854-861 (1990). Concentrate *in vacuo* to a residue and chromatograph (silica gel, 0.5%-1% $MeOH/CH_2Cl_2$) to give 5.9 g of the product compound.

Using nicotinic acid 1-N-oxide and substantially the same procedure as described for Preparative Example 8 the following compound is prepared:

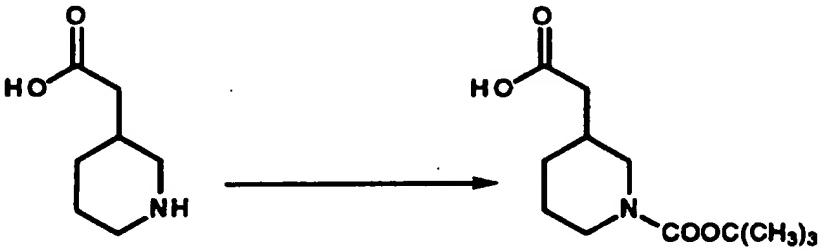


PREPARATIVE EXAMPLE 9

Step A:

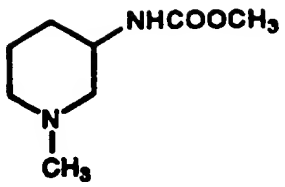
Hydrogenate 25 g (144 mmol) of 3-pyridylacetic acid hydrochloride for 144 hours using the procedure described in Preparative Example 3A to give 20 g of the product compound. Mass Spec.: $MH^+ = 144$.

Step B:



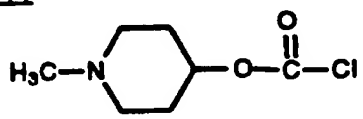
React 12 g (83.8 mmol) of the product of Step B for 148 hours using the procedure described in Preparative Example 3D, to give 17.5 g of the product compound. Mass Spec.: $MH^+ = 244.25$

PREPARATIVE EXAMPLE 10



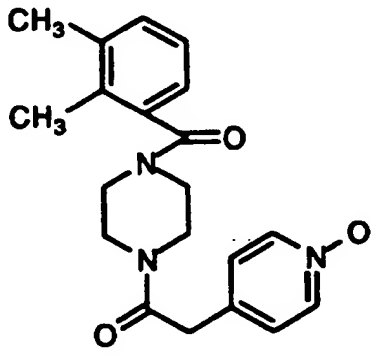
Combine 25 g (164.4 mmol) of methyl 3-pyridylcarbamate and 163.3 mL of 1N HCl (aqueous), stir until all of the solid dissolves, then hydrogenate over 10% Pd/C at 25°C at 55 psi for 220 hours. Filter, wash the solids with water and treat the combined filtrates with 150 mL of BioRad AG1X8 ion exchange resin (OH^-). Filter, wash the resin with water and concentrate the filtrate to a volume of 100 mL. Add 16.43 mL (197.3 mmol) of 37% formalin and hydrogenate over 10% Pd/C at 25°C at 55 psi for 89 hours. Filter, wash the solids with water and concentrate *in vacuo* to give 24.3 g of the title compound. Mass Spec.: MH^+ = 173.2.

PREPARATIVE EXAMPLE 11

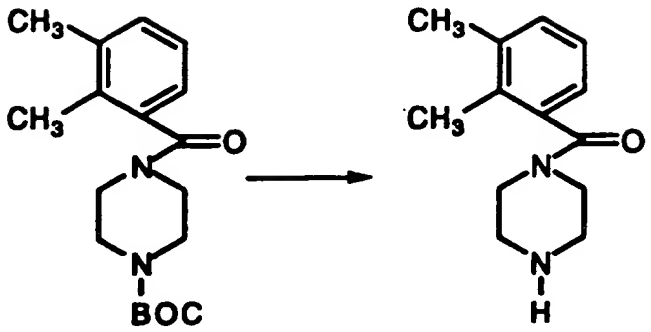


Combine 10 mL of dry CH_2Cl_2 and 914.6 mL (28.1 mmol) of a 1.93M solution of phosgene in toluene, cool to 0°C and slowly add (dropwise) a solution of 0.6484 g (5.62 mmol) of 4-hydroxy-1-N-methylpiperidine, 1.214 mL (15 mmol) of pyridine and 10 mL of dry CH_2Cl_2 over 10 minutes, then stir at 0° to 25°C for 2 hours. Purge excess phosgene with N_2 then concentrate in vacuo to give the title compound.

EXAMPLE 1

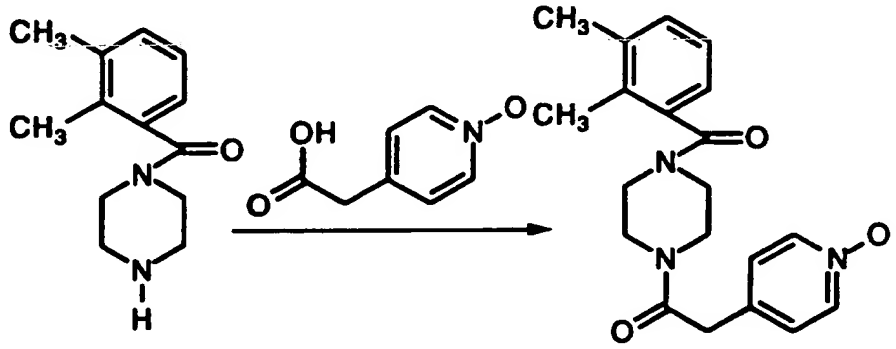


Step A:



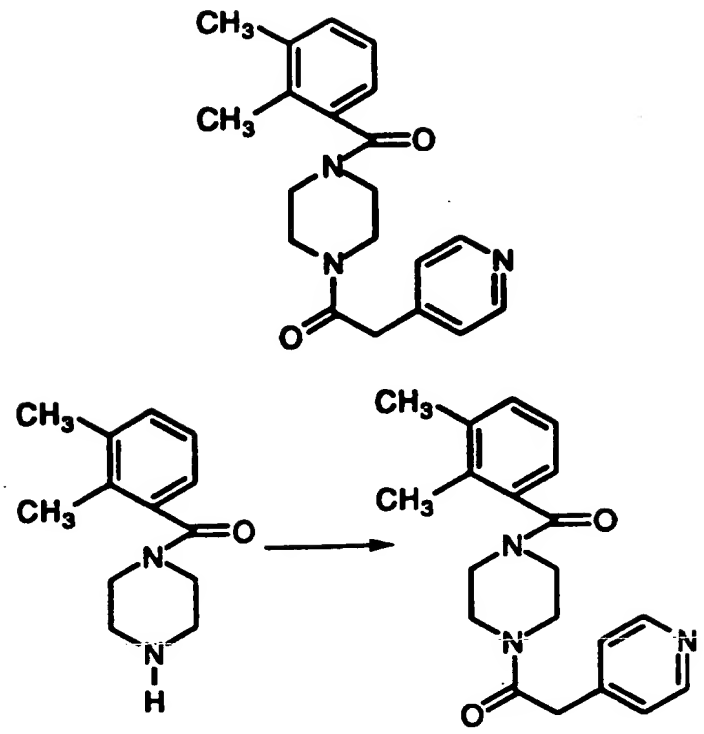
Dissolve 1-tert-butoxycarbonyl-4-(2,3-dimethylbenzoyl)-piperazine (described in WO 95/00497, p 45, Example 1) in dioxane saturated with HCl gas. After about one hour concentrate in vacuo and use the resulting HCl salt without purification.

Step B:



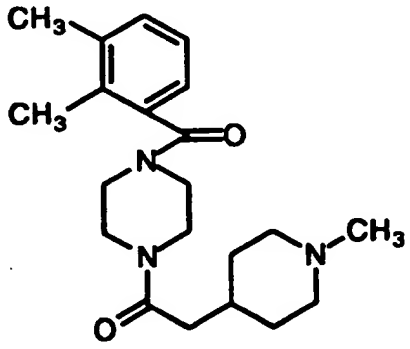
Dissolve the product of Step A in N,N-dimethyl formamide containing one equivalent of 1-hydroxybenzotriazole, (HOBT) one equivalent of 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (DEC), one equivalent of 4-pyridylacetic acid-1-N-oxide and one equivalent of N-methylmorpholine. When reaction is complete, about 4 hours, the reaction is poured into water and extracted with ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is chromotographed on silica gel using ethyl acetate-hexane to give the title compound.

EXAMPLE 2



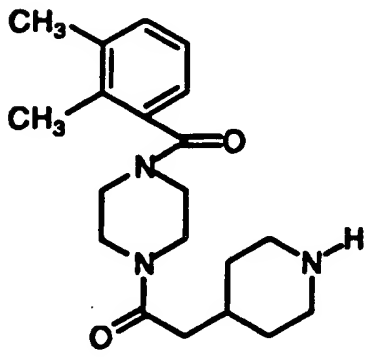
Perform the reaction of Example 1, Step B except use 4-pyridinylacetic acid instead of 4-pyridinylacetic acid-1-N-oxide to obtain the product.

EXAMPLE 3

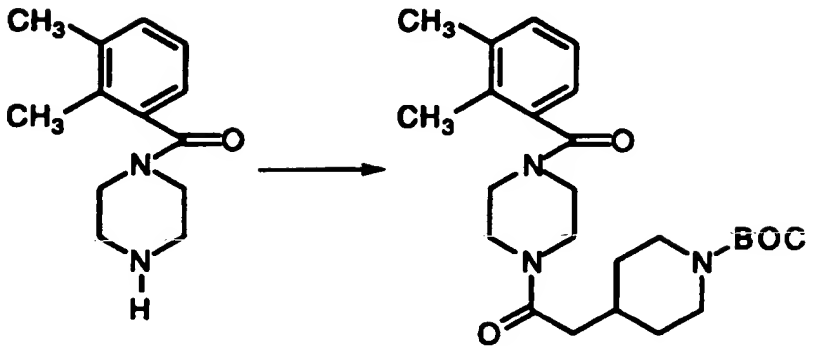


Perform the reaction of Example of 1, Step B except use N-methyl-4-piperidinylacetic acid (Preprative Example 3. Step C) instead of 4-pyridinylacetic acid-1-N-oxide to obtain the product.

EXAMPLE 4



Step A:

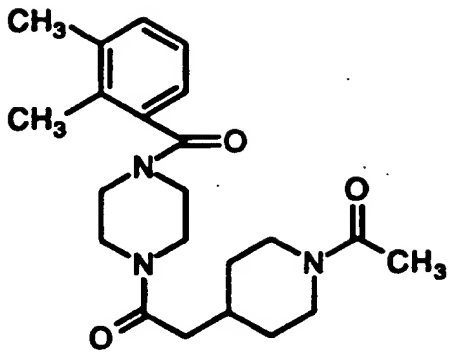


Perform the reaction of Example 1, Step B except use N-tert-butoxycarbonyl-4-piperidinylacetic acid (Preparative Example 3, Step D) instead of 4-pyridinylacetic acid-1-N-oxide to obtain the product.

Step B:

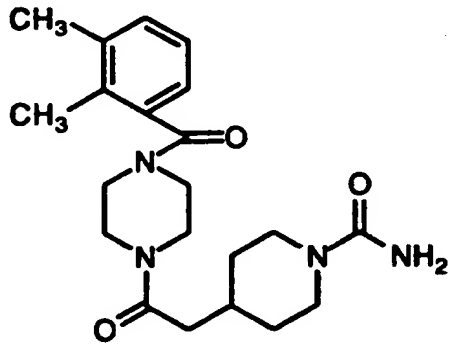
Dissolve the product of Step A in dioxane saturated with HCl gas and and allow to stir until complete, about 4 hours. Concentrate under vacuo. Partition between aqueous sodium bicarbonate solution and ethyl acetate. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo to give the title compound.

EXAMPLE 5



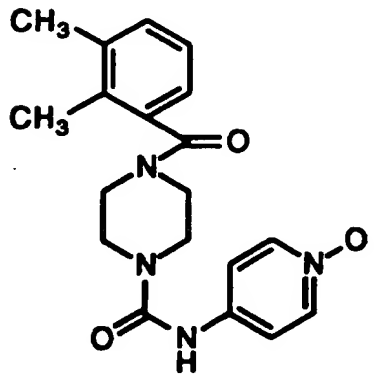
Dissolve the product of Example 4, Step B in pyridine and add 0.5 equivalent of acetic anhydride. Stir until complete, about 8 hours. Concentrate under vacuo. Dissolve in ethyl acetate, wash with brine, dry organic layer over magnesium sulfate, filter and concentrate in vacuo. Chromotograph on silica gel using ethyl acetate-hexane to give the title product.

EXAMPLE 6



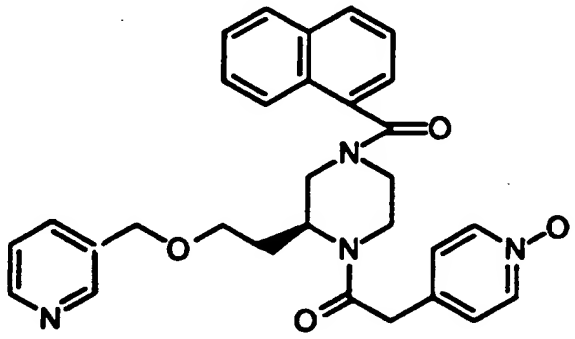
Dissolve the product of Example 4, Step B in methylene chloride and add excess trimethylsilylisocyanate. Stir under nitrogen for 18 hours. Wash with aqueous sodium bicarbonate solution. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo. Chromatograph the residue on silica gel using methanol-methylene chloride to give the product.

EXAMPLE 7



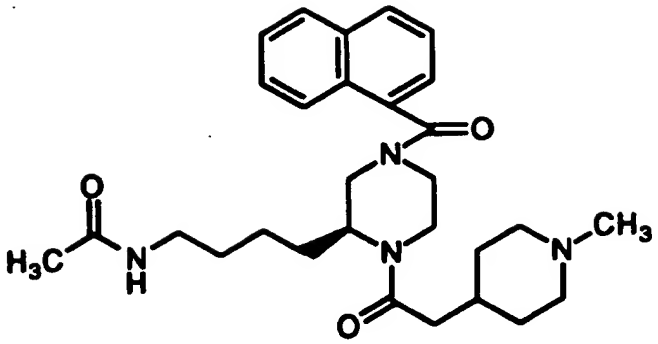
Dissolve the product of Preparative Example 8 in toluene and reflux for 2 hours. Cool to 25°C and add one equivalent of the product of Example 1, Step A and allow to stand for 18 hours. Concentrate and chromatograph on silica gel using chloroform-methanol to give the product.

EXAMPLE 8



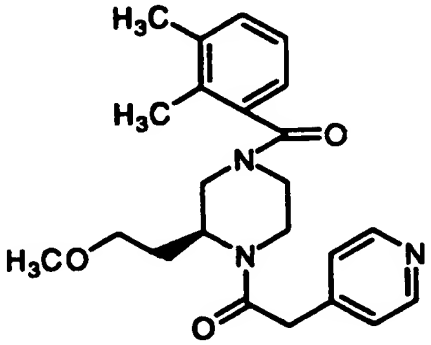
Dissolve 1-tert-butoxycarbonyl-(2(S)-2-(3-pyridyl-methoxyethyl)-4-(1-naphthoyl)piperazine (preparation described in WO 95/00497, Example 14) in dioxane saturated with HCl gas and allowed to stand until reaction is complete. Concentrate in vacuo and then react as described in Example 1, Step B to yield the product.

EXAMPLE 9



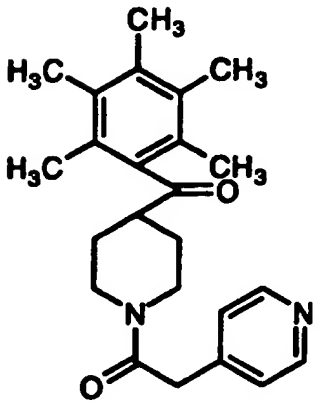
React 2(S)-4-acetamidobutyl)-4-(1-napthyl)- piperazine (preparation described in WO 95/00497, Example 27, Step G) with N-methyl-4-piperidinyl acetic acid (Preparative Example 4, Step C) by the process described in Example 3 to give the product.

EXAMPLE 10



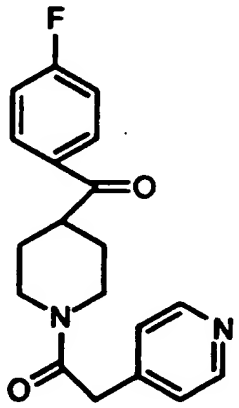
React 1-tert-butoxycarbonyl-4-(2,3-dimethylbenzoyl)-2(S)-(2-methoxyethyl)-piperazine (preparation described in WO 95/00497, Example 7, Step E) with 4-pyridylacetic acid using the process described in Example 2 to give the product.

EXAMPLE 11



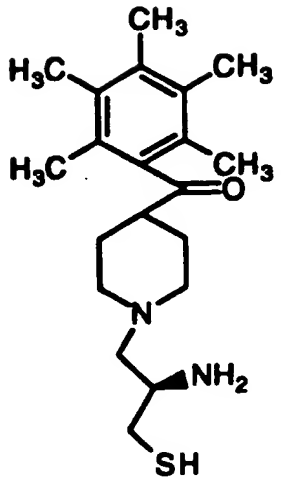
React 4-(pentamethylbenzoyl)-piperidine with 4-pyridylacetic acid by the process described in Example 2 and purify the crude product by silica gel chromatography using methanol-methylene chloride-amonia to give the product as a white solid, $M^+ = 379$.

EXAMPLE 12



React 4-(4-fluorobenzoyl)-piperidine with 4-pyridylacetic acid by the process described in Example 2 to give the product as a white solid, $M^+ = 327$.

EXAMPLE 13



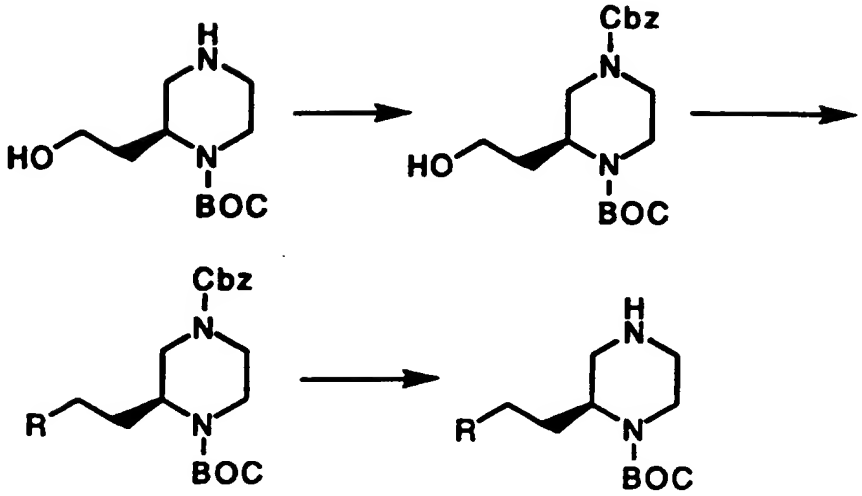
Step A:

Dissolve one equivalent of 4-(pentamethylbenzoyl)-piperidine in N,N-dimethyl formamide containing one equivalent of sodium triacetoxyborohydride and crushed molecular sieves. Cool this solution to 0°C and add dropwise, a solution of 1 equivalent of 2(R)-tert-butoxycarbonylamino-3-triphenylmethylthiopropanal (preparation described in WO 95/00497, Example 1, Step C, and by O.P. Goel, et al. Organic Synthesis (1988), 67, 69-75) in N,N-dimethylformamide. Allow reaction to warm to 20°C and stir under nitrogen for 2 hours. Concentrate in vacuo and partition the residue between ethyl acetate and saturated sodium bicarbonate solution. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo.

Step B:

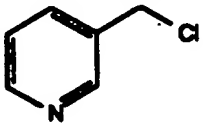
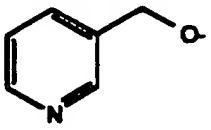
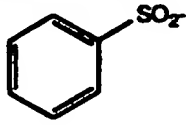
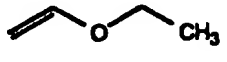
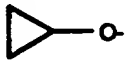
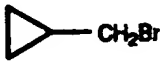
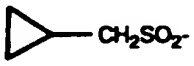
Dissolve the product from Step A in methylene chloride and add five equivalents of triethylsilane. To this solution add trifluoroacetic (10 equivalents) and stir the reaction at 20°C for 30 min. Concentrate in vacuo and partition between water and hexane. Chromatograph the water layer on a C18 HPLC column using acetonitrile water and 0.1% trifluoroacetic acid. The combined fractions are evaporated, dissolved in water and passed through a Biorad AG 3x4 (Cl^-) ion exchange column to give the product as a hydrochloride salt.

EXAMPLE 14

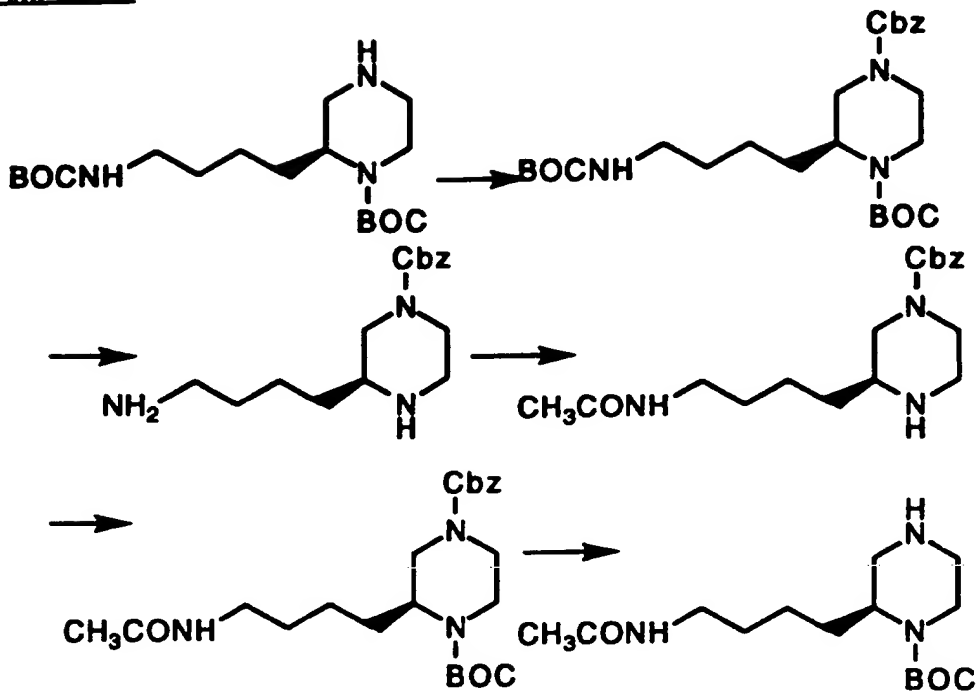


The title compound from Example 13A (WO 95/00497) is reacted with benzyloxycarbonyl chloride under standard conditions known to one skilled in the art, to give the N-Cbz protected alcohol shown above. After purification in the usual way the latter may be reacted with a variety of reagents shown in Column 1 of Table 1 to give the corresponding N-Cbz protected intermediates where R is as defined in Column 2 of Table 1.After purification in the usual way the latter may be deprotected using mild catalytic hydrogenation procedures known in the art, to give after suitable purification, the final desired intermediates shown in Column 2 of Table 1.

TABLE 1

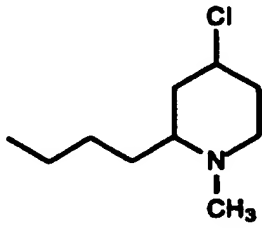
Column 1	Column 2
 and NaH	 Prepared as described in Example 14A (WO 95/00497) Example 6.
$C_6H_5SSC_6H_5$ + $(n\text{-}Bu)_3P$	R=  Prepared as described in Example 20B and 20C (WO 95/00497) Example 7.
(i)  + $Hg(OAc)_2$ + CH_3COOH (ii) CH_2I_2 + Et_2Zn	R=  Prepared as described in Examples 26A and 26B (WO 95/00497) Example 8
(i) EtOCON=NCOOEt + $(C_6H_5)_3P$ + CH_3COSH (ii) NH_3 + CH_3OH +  (iii) Mg monoperphthalic acid + CH_3OH	R =  Prepared as described in Examples 29A, 29B and 29C (WO 95/00497) Example 9
n-C_3H_7I + NaH	n-C_3H_7O- Prepared as described in Example 13C (WO 95/00497) Example 10

EXAMPLE 15

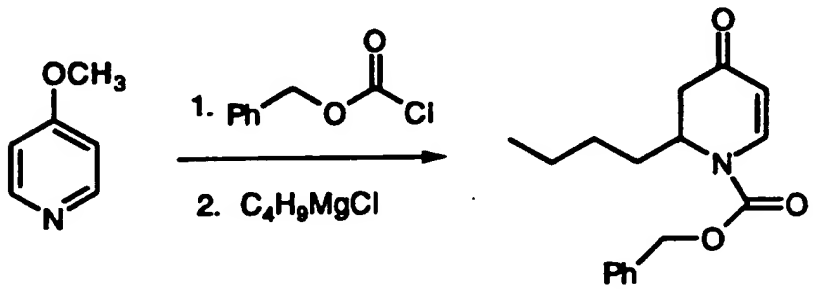


The title compound from Example 27D (WO 95/00497) is converted by the scheme shown above using standard procedures known to one skilled in the art into 1-*tert*-butoxycarbonyl-2(S)-(4-acetylaminobutyl)piperazine.

EXAMPLE 16



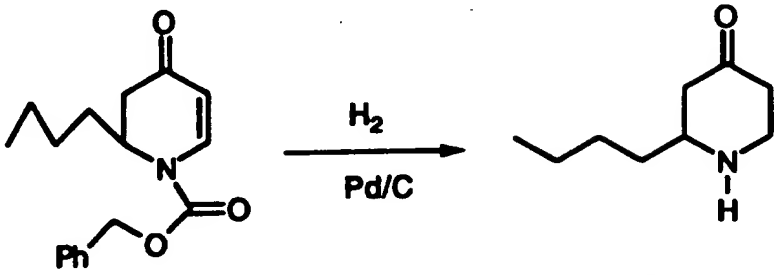
Step A:



As described by D.L. Comins, et al., Tet Lett 4549 (1986). Dissolve 4-methoxypyridine in THF and cool to -23°C. Add benzylchloroformate dropwise (1 equivalent) followed by 1 equivalent of butyl magnesium chloride in THF

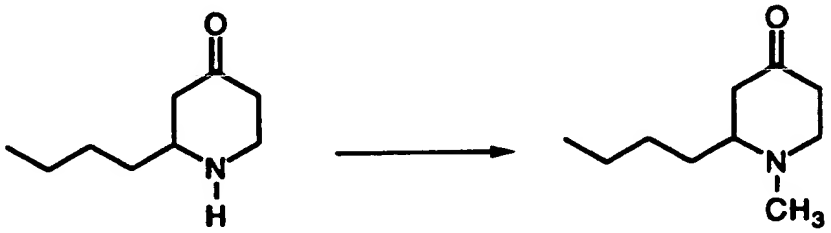
added dropwise. Pour into 10% hydrochloric acid and xtract with th r. Dry over $MgSO_4$ and concentrate.

Step B:



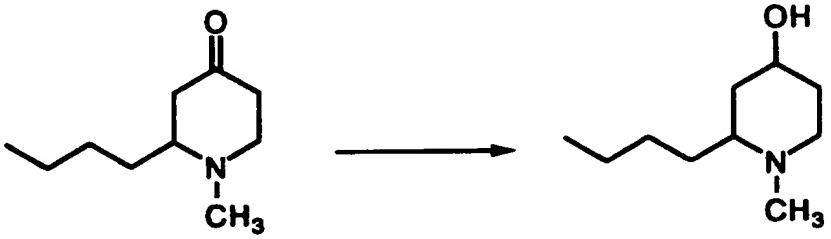
Dissolve the product of Step A in ethanol containing 10% palladium on carbon and hydrogenate at 60 psi. Filter and concentrate in vacuo to obtain the product.

Step C:



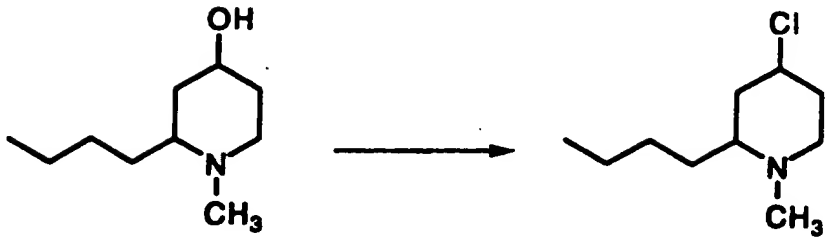
Dissolve the product of Step B in tetrahydrofuran, cool to 0°C under nitrogen and add one equivalent of sodium hydride. After stirring for 15 min., one equivalent of methyl iodide is added. Stir reaction for 15 min., concentrate under vacuo and chromatograph on silica gel using methanol-methylene chloride.

Step D:



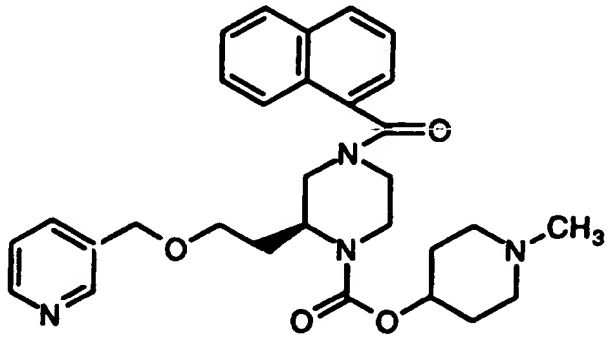
Dissolve the product of Step C in ethanol and add an excess of sodium borohydride. Concentrate in vacuo. Partition between water and ethyl acetate. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo.

Step E:



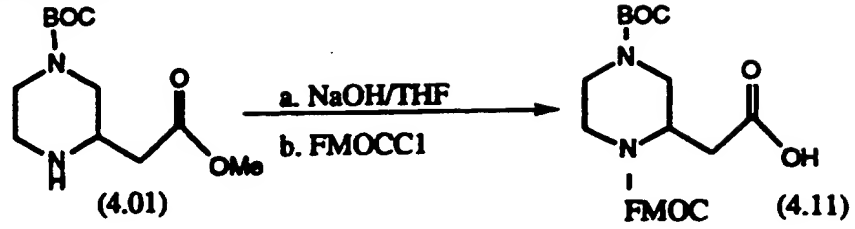
Dissolve the product of Step D in pyridine containing an excess of thionyl chloride. Stir for 18 hours and concentrate in vacuo. Partition between ethyl acetate and aqueous sodium bicarbonate. Dry the organic layer over magnesium sulfate, filter and concentrate in vacuo to obtain the product.

EXAMPLE 17.



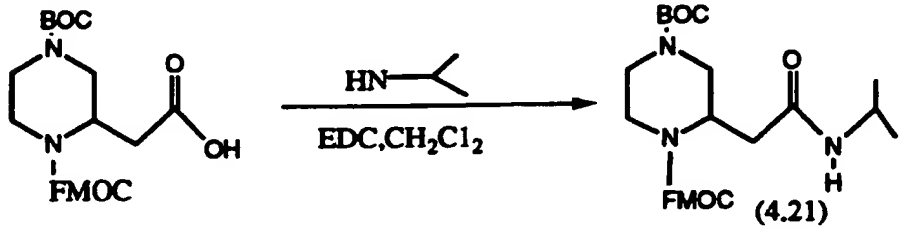
Dissolve 2(S)-2-(3-pyridyl-methoxyethyl)-4-(1-naphtholyl)piperazine (preparation described in WO 95/00497, Example 14, Step B) in methylene chloride containing one equivalent of triethylamine and cool to 0°C under nitrogen. Add one equivalent of the product of Preparative Example 11 and allow the reaction to warm to room temperature. Stir at 25°C until reaction is complete, about 10 hours. Concentrate in vacuo and chromatograph on silica gel using chloroform-methanol-ammonia to give the product.

EXAMPLE 18.



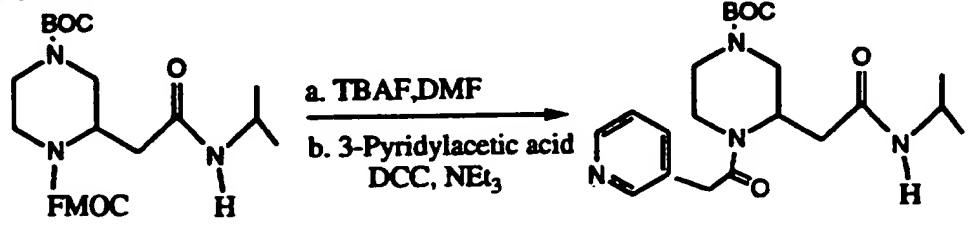
(4.01) (4.11)

To the solution of above methyl 4-N-BOC-2-piperazine acetate (4.0) (5.2 g, 20 mmol) in THF (60 mL) is added 1N NaOH (60 mL). The reaction mixtures is stirred at room temperature for 6 hours, cooled to 0°C and acidified to pH=9-10 by 10% HCl followed by the addition of FMOC-Cl (5.2 g, 20 mmole). The pH of the reaction mixture is kept at 9-10 by adding 1N NaOH. After room temperature for 6 hours, reaction mixture is acidfied by 10% HCl to pH=1 and extracted with ethyl acetate twice. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated to give 4-N-BOC-1-N-FMOC-2-piperazine acetic acid (4.1) (8.56 g, 89%) as a white foam.



(4.11) (4.21)

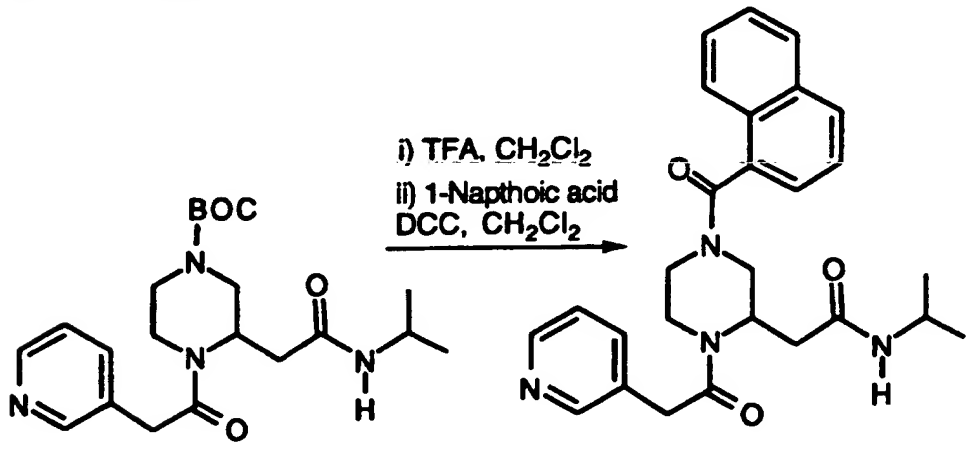
To the above 4-N-BOC-1-N-FMOC-2-piperazine acetic acid (4.1) (460 mg, 1 mmol) in 5 mL CH_2C1_2 is added EDC (230 mg, 1.2 mmol) followed by the addition of isopropyl amine (130 µL, 1.5 mmol). After stirring at room temperature for 6 hours, the reaction mixture is treated with 1N HCl (10 mL) and ethyl acetate (30 mL). The organic layer is separated, washed with saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated to provide isopropyl 4-N-BOC-1-N-FMOC-2-piperazine acetamide (4.2) (454.6 mg, 90%) as a white foam.



(4.21) (5.11)

To the solution of isopropyl 4-N-BOC-1-N-FMOC-2-piperazine acetamide (4.2) (150 mg, 0.3 mmol) in DMF is added TBAF (142 mg, 0.45 mmol). After stirring at room temperature for 1/2 hour, the reaction mixture is tr at d with 1N

HC1 (5 mL) and ethyl acetate (10 ML). The aqueous layer is washed with thyl acetate once, basified with saturated K_2CO_3 and extracted three tim s with ethyl acetate. The combined organic layers are dried ver $MgSO_4$ and concentrated to afford the desired intermediate isopropyl-4-N-BOC-2-piperazine acetamide which is used for the following reaction without further purification. To the solution of 3-pyridylacetic acid (52 mg, 0.3 mmol) and triethyl amine (85 µL, 0.6 mmol) in 5 mL CH_2Cl_2 is added DCC (75 mg, 0.36 mmol) followed by the addition of isopropyl-4-N-BOC-2-piperazine acetamide in 2 mL CH_2Cl_2. The reaction mixture is stirred at room temperature for 8 hours and concentrated and purified by flash chromatography to give (5.1) (106.2 mg, 88%) as a colorless oil. R_f=0.4 (10% MeOH in CH_2Cl_2).

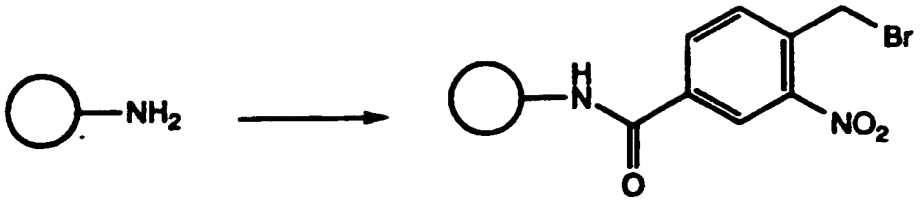


(5.11) (1.1)

To a solution of (5.1) (0.1g, 0.197 mmol) in DCM(6 mL) is added TFA (2 mL). The reaction mixture stirred at room temperature for one hour and is then evaporated to dryness *in vacuo*. The residue is dissolved in ethyl acetate (50 mL) and washed with water (40 mL). The aqueous phase is then basified with solid sodium carbonate and extracted with chloroform (5 x 20 mL). The organic phase is dried over $MgSO_4$ and concentrated *in vacuo* affording the deprotected material as an oil in mass 0.069g (84%). To a solution of the oil (0.02g, 0.07 mmol) in DCM (1 mL) is added DCC (0.021g, 0.1 mmol) and 1-naphthoic acid (0.017g, 0.1 mmole). The reaction mixture is stirred at room temperature for 8 hours and is then purified directly by flash chromatography (SiO_2, 5% methanol in DCM) affording (1.0) as an oil in mass 0.03g (94%)

Example 19.

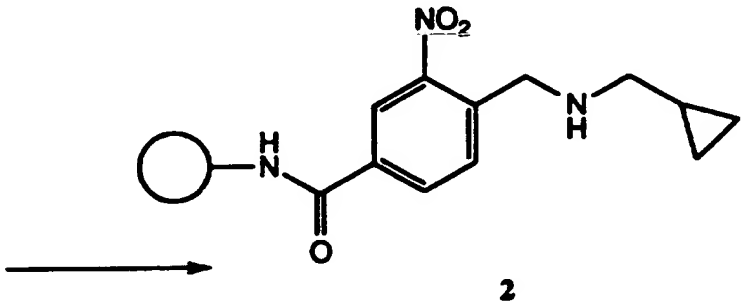
Preparation of 1



1

To a suspension of Tentagel S® NH_2 Resin (Rapp Polymere Gmbh, Germany) (1.0g, 0.28 mmol/g loading, 0.28 mmol) in DCM (10mL) in a Merrifield reaction vessel was added 4-(bromomethyl)-3-nitrobenzoic acid (1.12 mmol, 0.29g), HOBT (1.12 mmol, 0.15g) and DIC (1.68 mmol, 0.21g, 0.26mL). The resin shook at room temperature for 16h and was then washed with DCM (4 x 10mL) and THF (3 x 10 mL).

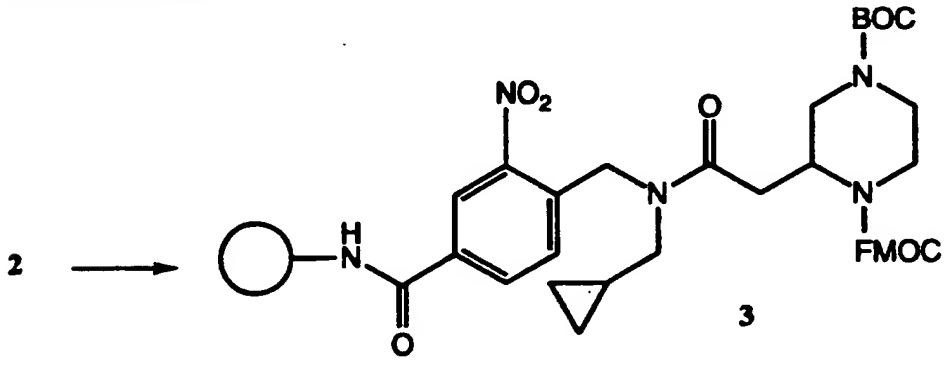
Preparation of 2



1 2

The resin (0.28 mmol theoretical loading) was suspended in THF (10 mL) and treated with (aminomethyl)cyclopropane (5.6 mmol, 0.40g, 0.49 mL) at room temperature for 16h. The resin was then washed with THF (2 x 10 mL).

Preparation of 3

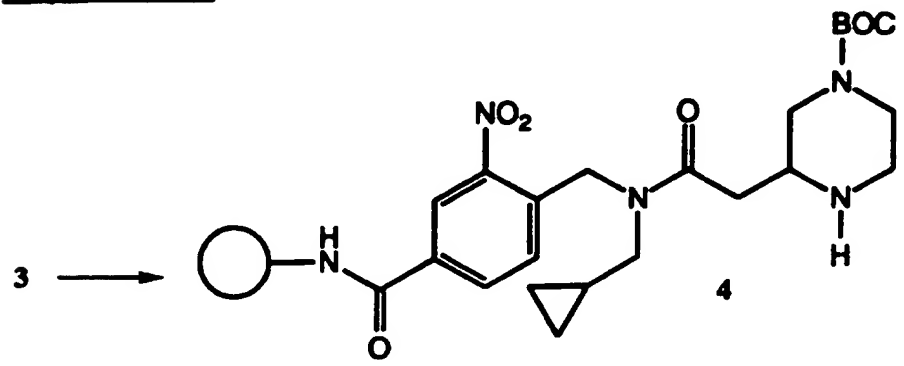


2 3

The resin (0.28 mmol theoretical loading) is suspended in DCM (10mL) and r acted with 1-N-FMOC-4-BOC piperazine-2-acetic acid (1.12 mmol, 0.52g), HATU (1.12 mmol, 0.43g) and N,N-diisopropyethylamin (2.24 mmol, 0.29g,

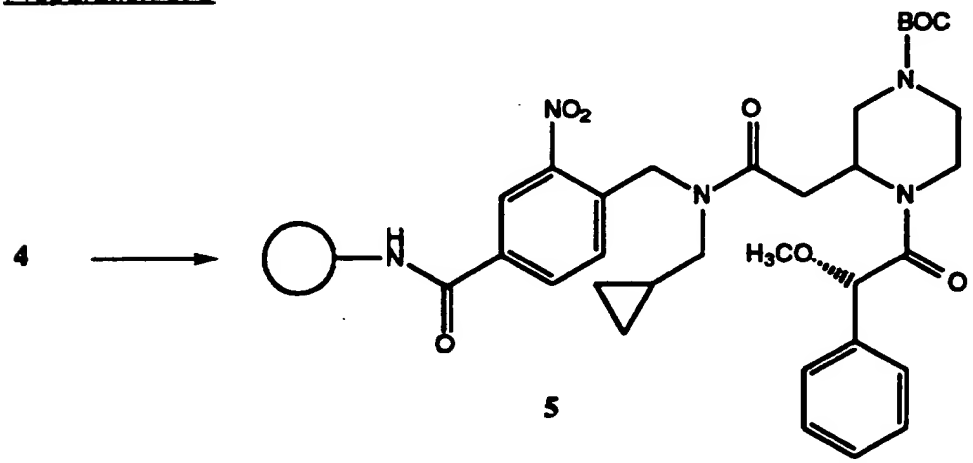
0.39mL). Th resin is shaken at room temperatur for 16 h and is then washed with DCM (4 x 10 mL). The resin is then retreated with th sam mixture of reagents in a second coupling cycle of 16h. The resin is then washed with DCM (6 x 10mL).

Preparation of 4



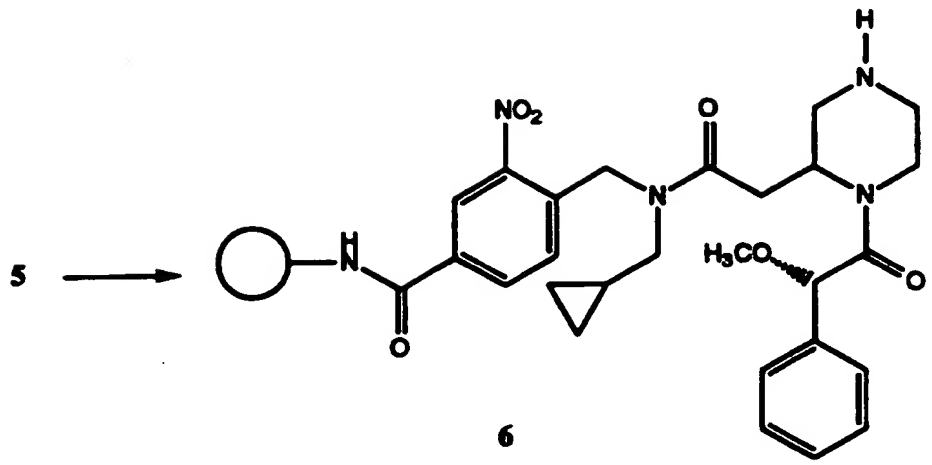
The resin (0.28 mmol theoretical loading) is washed once with DMF (10 mL) and is then treated with a 30% solution of piperidine in DMF (total volume = 10 mL) at room temperature for 30 min. The resin is then washed with DMF (10 mL), methanol (2 x 10 mL) and DCM (3 x 10 mL).

Preparation of 5



The resin (0.28 mmol theoretical loading) is suspended in DCM (10mL) and treated with (S)-(+)-α-methoxyphenylacetic acid (1.12 mmol, 0.19g), HATU (1.12 mmol, 0.43g) and N,N-diisopropylethylamine (2.24 mmol, 0.29g, 0.39 mL). The resin is shaken at room temperature for 16h and then washed with DCM (4 x 10 mL).

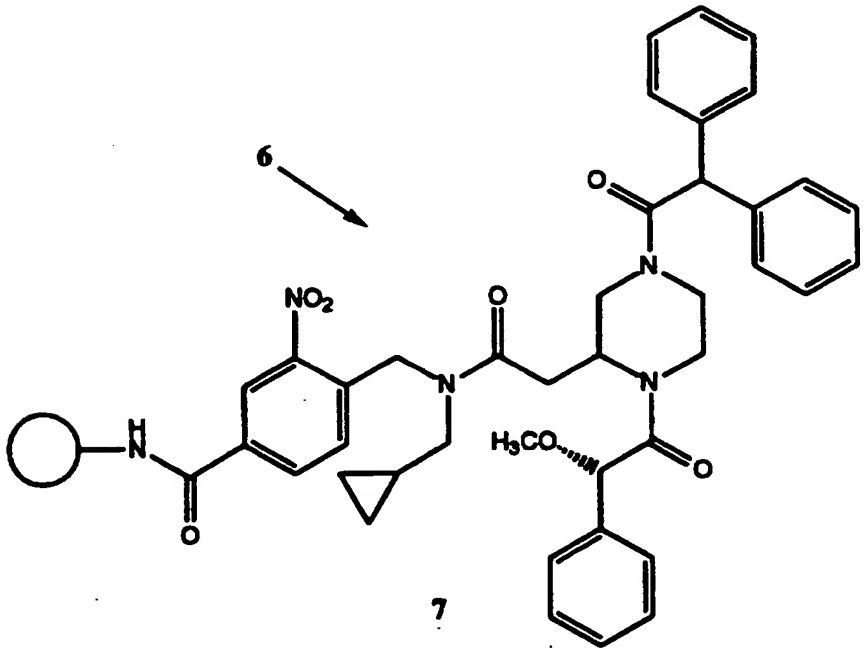
Preparation of 6



6

The resin (0.28 mmol theoretical loading) is treated with a 30% solution of TFA in DCM (10 mL) at room temperature for 1h. The resin is then washed with DCM (2 x 10 mL) and methanol (3 x 10 mL) and then treated with a 20% solution of triethylamine in methanol (10 mL) for 30 min. The resin is then washed with methanol (2 x 10 mL) and DCM (4 x 10 mL).

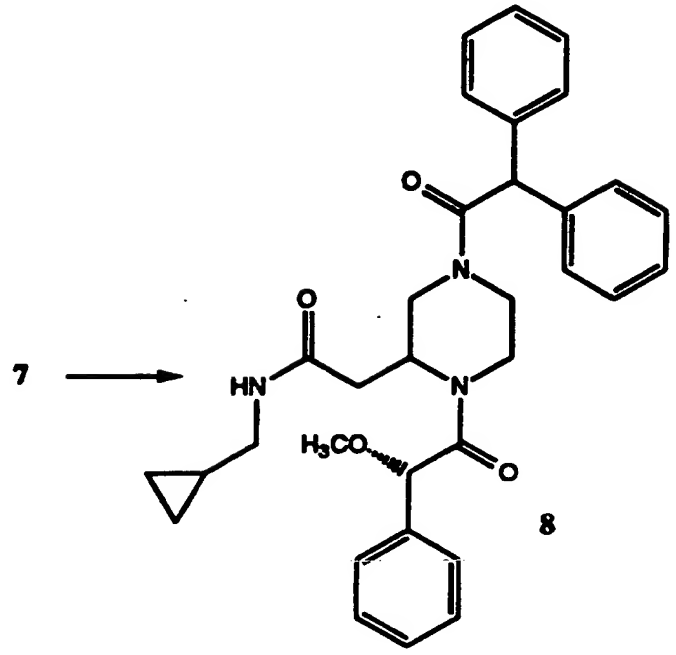
Preparation of 7



7

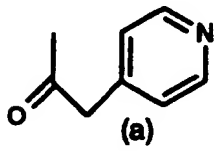
The resin (0.28 mmol theoretical loading) is suspended in DCM (10 mL) and treated with diphenylacetic acid (1.26 mmol, 0.27g), HATU (1.26 mmol, 0.48g) and N,N-diisopropylethylamine (2.52 mmol, 0.33g, 0.44 mL). The resin is shaken at room temperature for 16h and then washed with DCM (5 x 10 mL), DMF (3 x 10 mL) and methanol (3 x 10 mL).

Preparation of 8

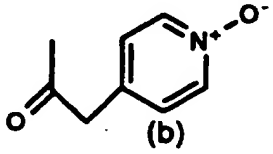


The resin (0.28 mmol theoretical loading) is washed from the Merrifield vessel into a 25 mL round-bottomed flask with methanol (10 mL) and photolysed (UVP Blak-Ray lamp, 360nm) for 3h. The resin is filtered and washed with methanol (3 x 10 mL) and DCM (3 x 10 mL). The solvent and washings are combined and evaporated to dryness *in vacuo* giving compound 8.

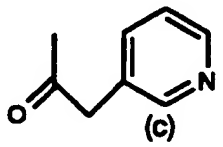
Representative R^1 groups in compounds (1.0) and (1.1) can include the following:



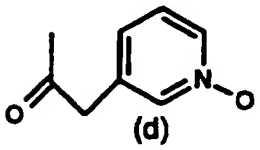
(a)



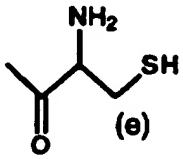
(b)



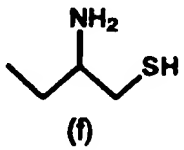
(c)



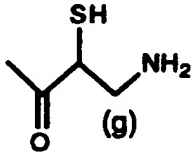
(d)



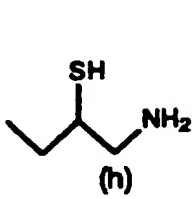
(e)

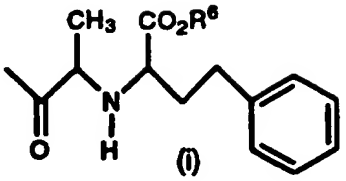


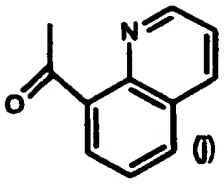
(f)

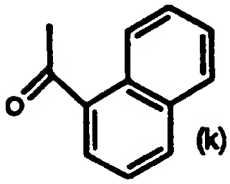


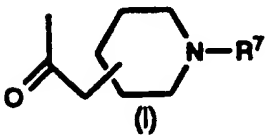
(g)

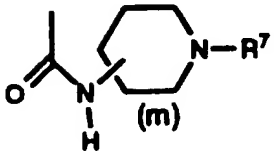

(h)

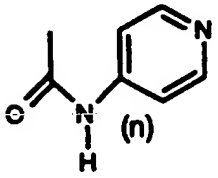

(i)

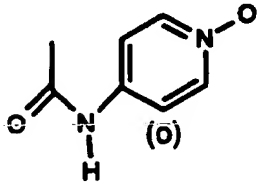

(j)

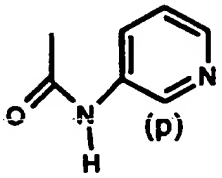

(k)


(l)

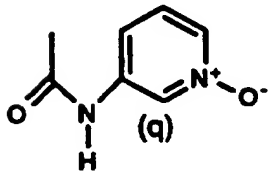

(m)

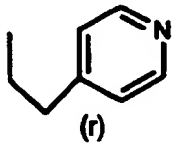

(n)

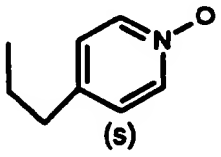

(o)

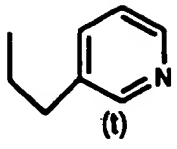

(p)

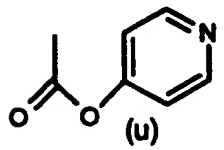
5

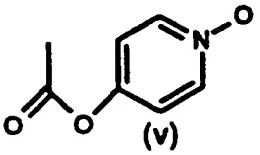

(q)

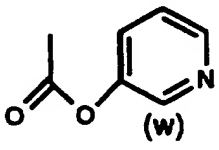

(r)


(s)

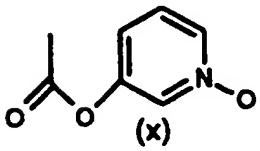

(t)

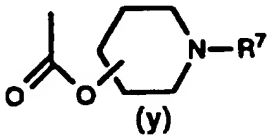

(u)

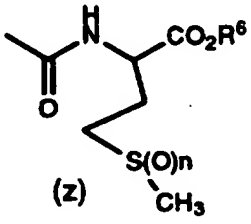

(v)


(w)

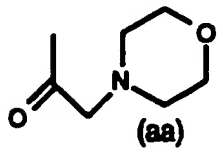
10

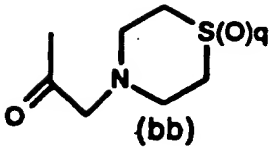

(x)

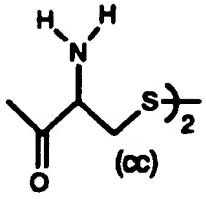

(y)

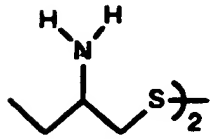

(z)

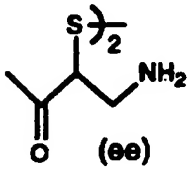
62

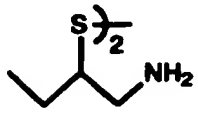

(aa) ;

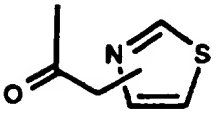

(bb) ;

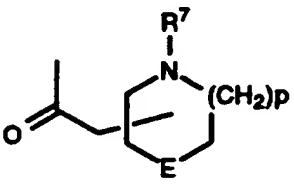

(cc) ,

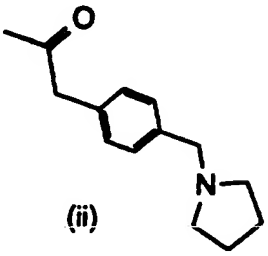

(dd) ,

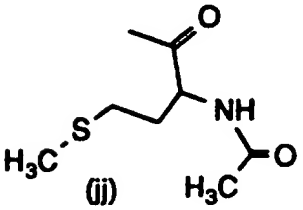

(ee) ;

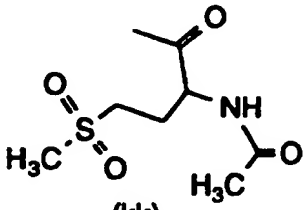

(ff) ;

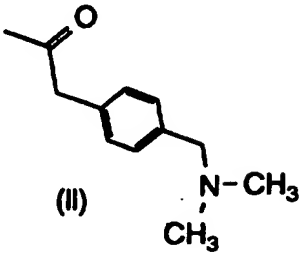

(gg) ;

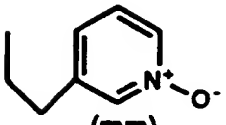

(hh) ;

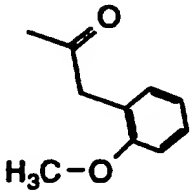

(ii) ;

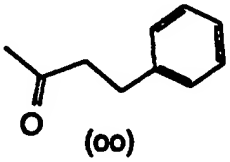

(jj) ;

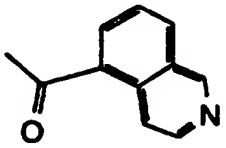

(kk) ;

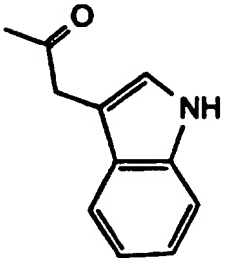

(ll) ;

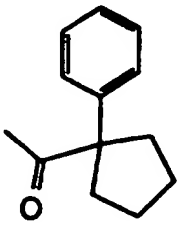

(mm) ;

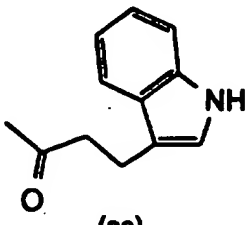

(nn) ;

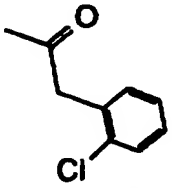

(oo) ;

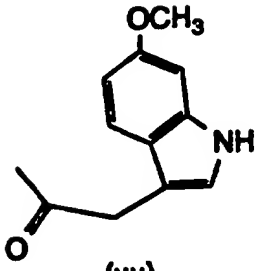

(pp) ;

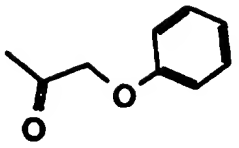

(qq) ;

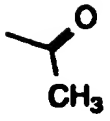

(rr) ;

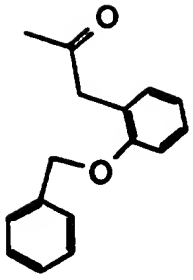

(ss) ;

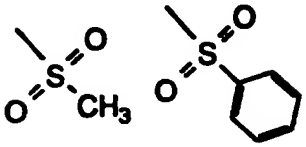

(tt) ;


(uu) ;

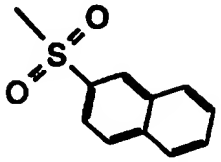

(vv) ;

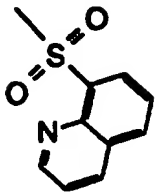

(ww) ;

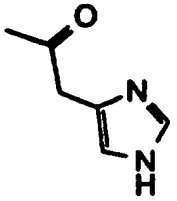

(xx) ;

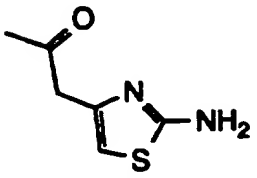

(yy) ;

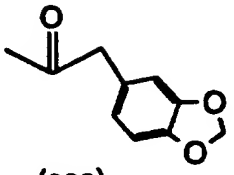
(zz) ;

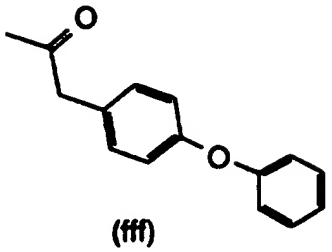

(aaa) ;

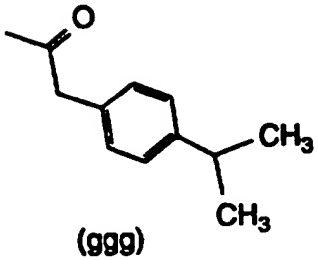

(bbb) ;

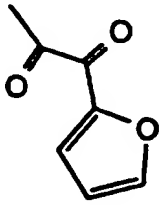

(ccc) ;

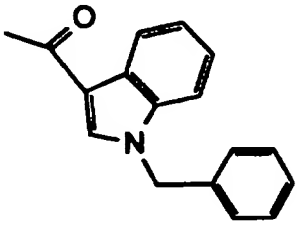

(ddd) ;

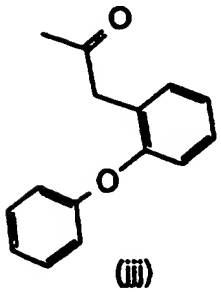

(eee) ;

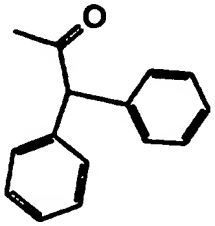

(fff) ;

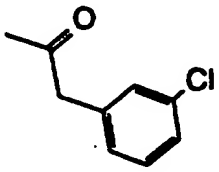

(ggg) ;

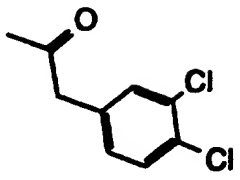

(hhh) ;

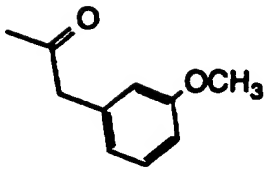

(iii) ;

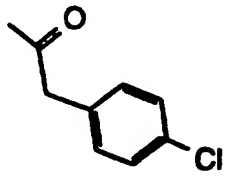

(jjj) ;


(kkk) ;


(lll) ;


(mmm) ;


(nnn) ;


(ooo) .

wherein p is 1 or 2;

q is 0, 1 or 2;

E is CH_2 or NR^7;

R^6 is H or C_1 to C_6 alkyl;

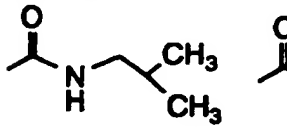
R^7 is H, C_1 to C_6 alkyl, haloalkyl, $-C(O)R^{11}$, $-C(O)OR^{13}$, $-C(O)NR^{14}R^{15}$ or an acyl radical of a naturally occuring amino acid; wherein

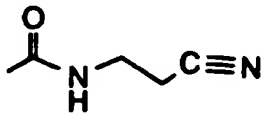
R^{11} is C_1 to C_6 alkyl, C_1 to C_6 alkoxy or $-NHR^{12}$ and

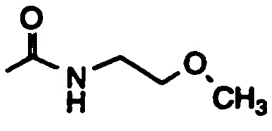
R^{12} is C_1 to C_6 alkyl or H;

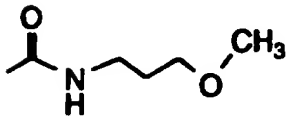
with the proviso that when X^1 is N and R^2 is C_1 to C_6 alkyl or aralkyl, then R^1 is not (e) or (f).

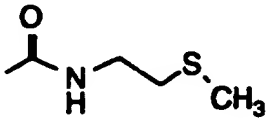
Representative R^2 or R^3 groups in compounds (1.0) and (1.1) can include the following.

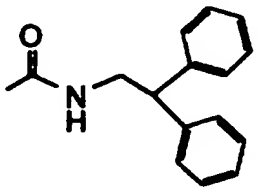

(0.222) ;

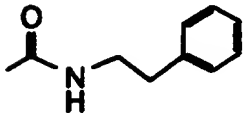

(0.223) ;

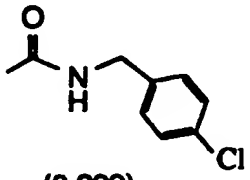

(0.224) ;

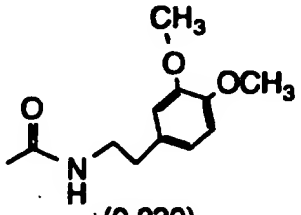

(0.225) ;

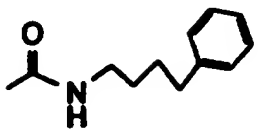
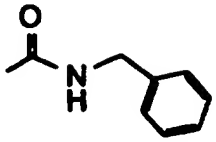
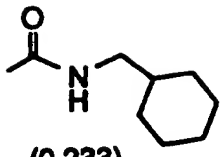
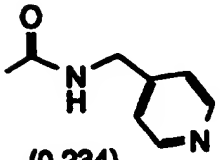
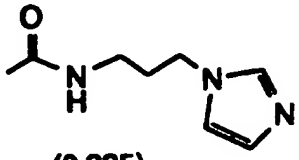
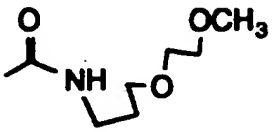
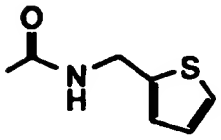
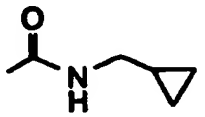
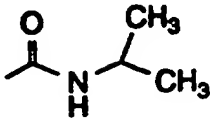
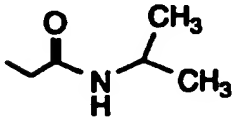
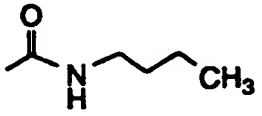
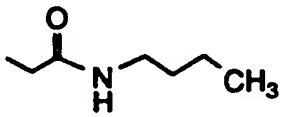
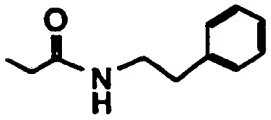
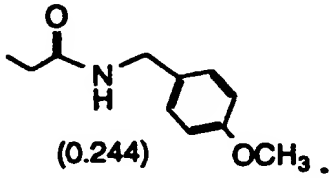
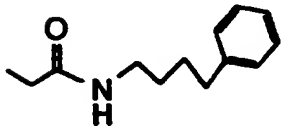
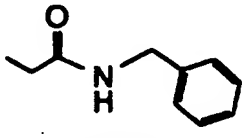
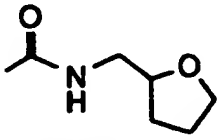
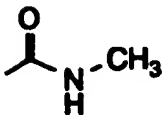
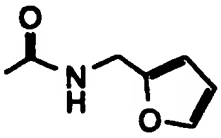
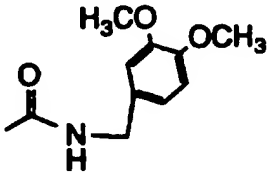

(0.226) ;


(0.227) ;


(0.228) ;


(0.229) ;


(0.230) ;


(0.231) ;

(0.232) ;

(0.233) ;

(0.234) ;

(0.235) ;

(0.236) ;

(0.237) ;

(0.238) ;

(0.239) ;

(0.240) ;

(0.241) ;

(0.242) ;

(0.243) ;

(0.244) ;

(0.245) ;

(0.246) ;

(0.247) ;

(0.248) ;

(0.249) or

(0.250) .

For preparing pharmaceutical compositions from the compounds described by this inv ntion, inert, pharmaceutically acceptable carriers can be ither solid or liquid. Solid form preparations include powders, tablets,

dispersible granules, capsules, cachets and suppositori s. The powd rs and tablets may be comprised of from about 5 to about 70 percent activ ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cach ts and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable orally, or parentally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, transdermal and topical routes of administration. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of activ compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more pref rably from about 1. mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon th requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

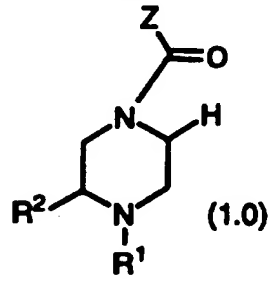
While the present invention has been described in conjunction with th specific embodiments set forth above, many alt matives, modifications and variations thereof will be apparent to thos of ordinary skill in the art. All such alt matives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Assays

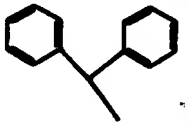
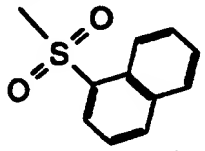
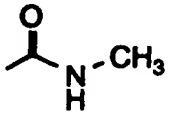
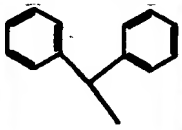
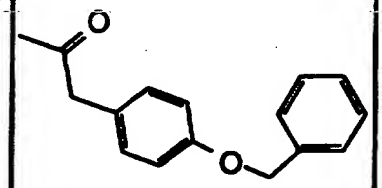
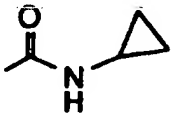
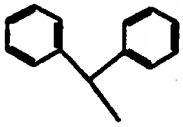
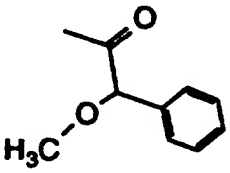
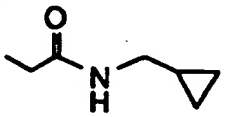
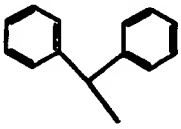
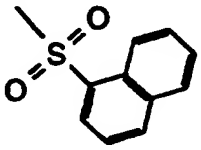
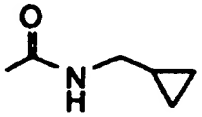
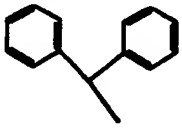
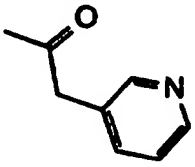
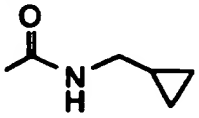
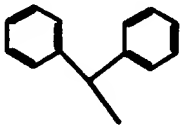
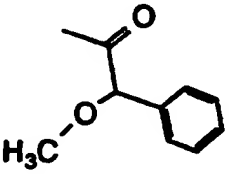
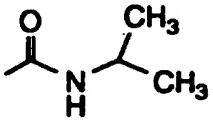
Measurements of pharmacological activity of the present compounds can be made based upon a cell-based assay (i.e. FPT IC_{50}), cell mat assay (GGPT IC_{50}) or in vitro tumor activity (Cos Cell IC50) as described by the methods in WO95/10516.

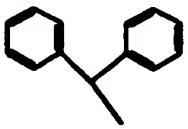
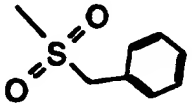
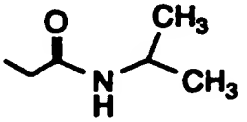
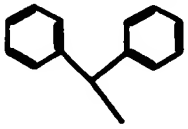
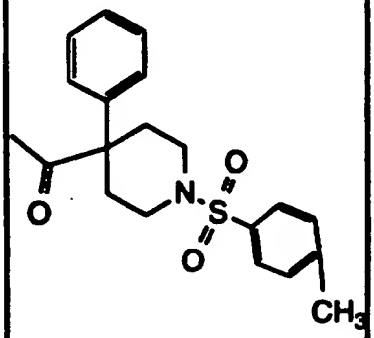
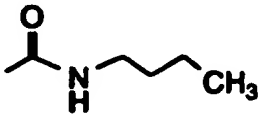
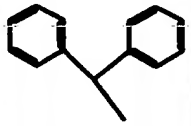
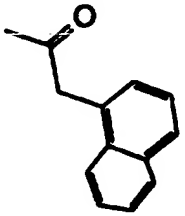
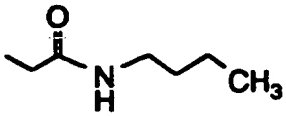
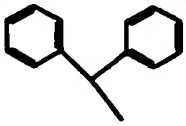
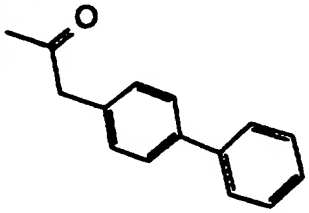
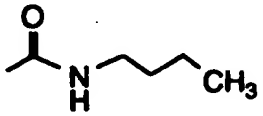
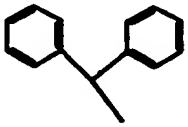
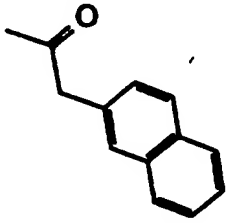
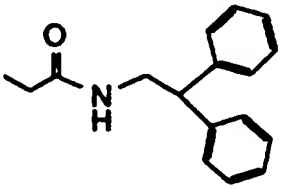
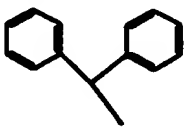
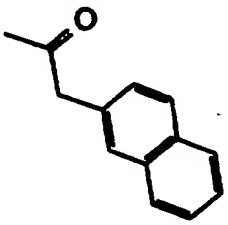
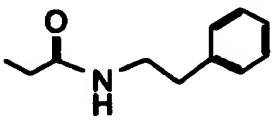
Under the test protocols employed, there were certain compounds within the scope of the present invention which did not exhibit activity. It is believed that such compounds would exhibit activity under a different test protocol.

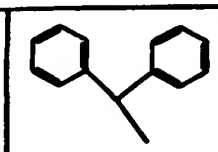
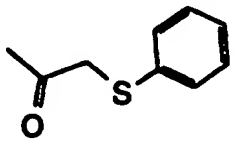
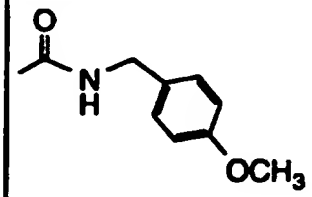
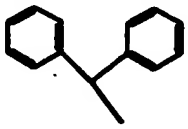
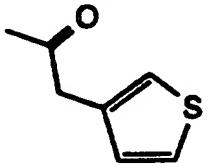
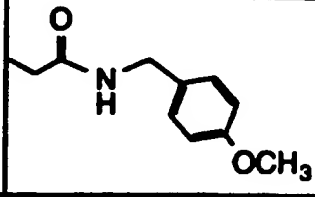
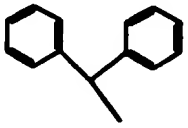
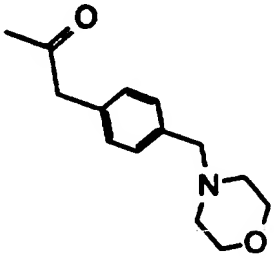
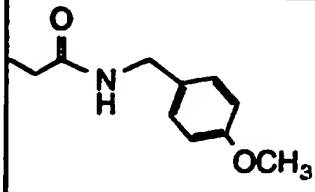
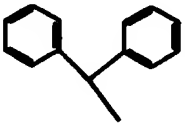
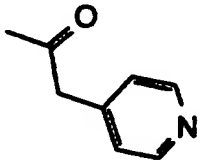
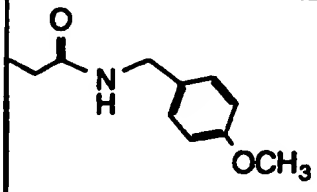
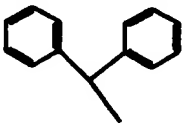
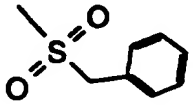
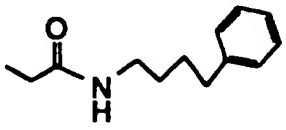
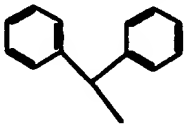
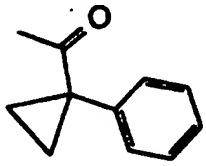
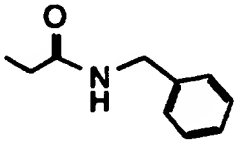
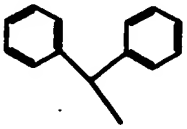
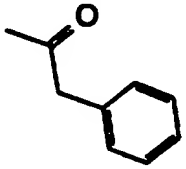
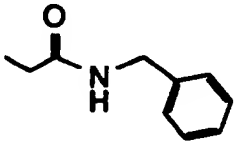
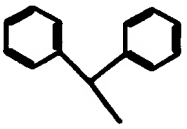
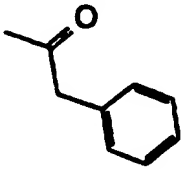
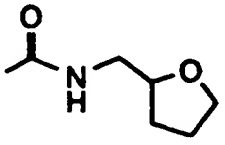
The following compounds exhibit d biological activity at concentrations below 10 micromoles (um) using an in vitro assay measuring th inhibition of FTas .

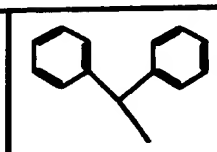
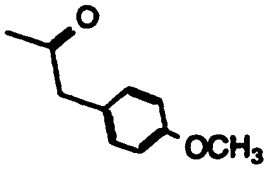
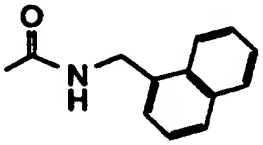
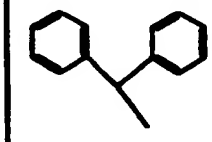
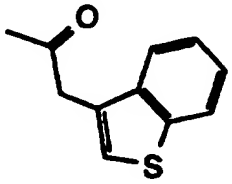
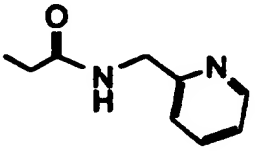
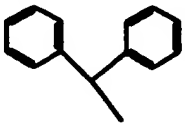
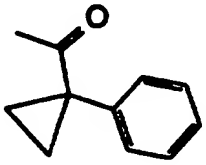
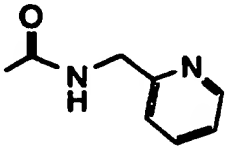
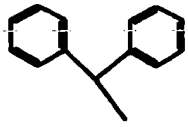
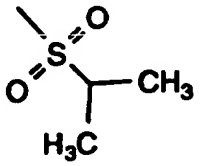
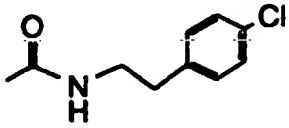
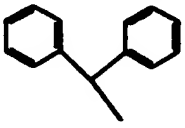
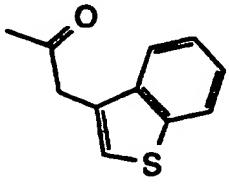
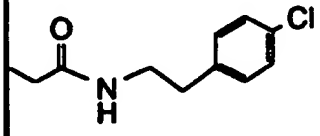
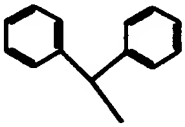
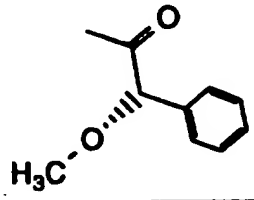
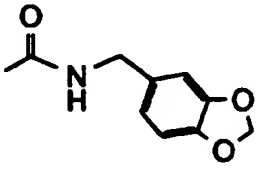
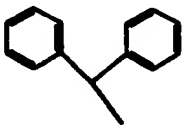
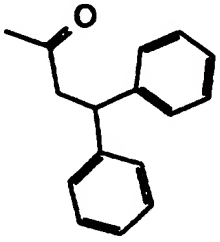
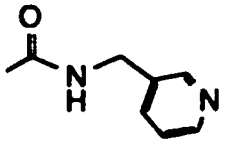


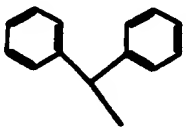
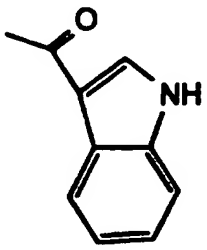
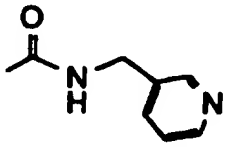
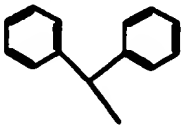
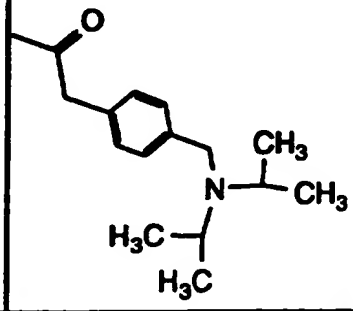
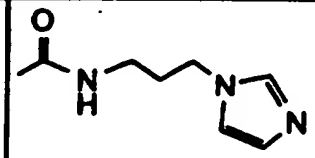
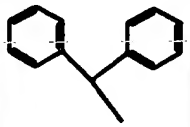
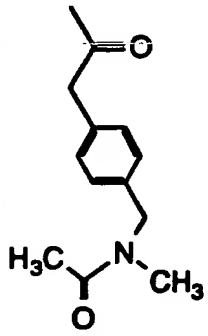
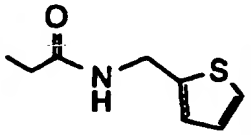
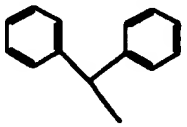
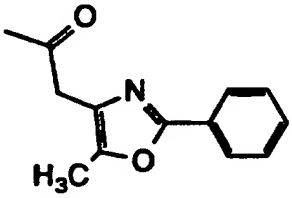
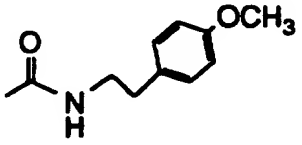
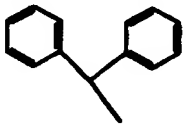
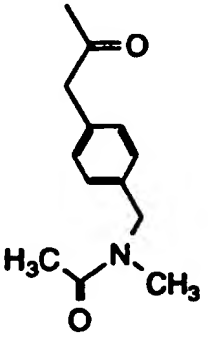
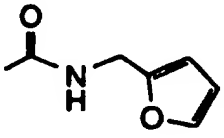
(1.0)

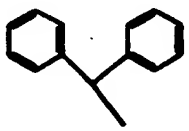
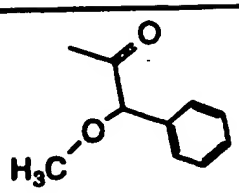
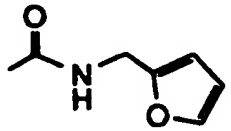
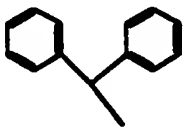
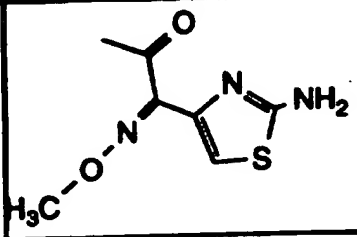
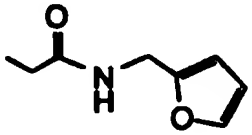
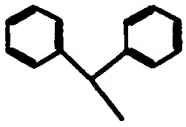
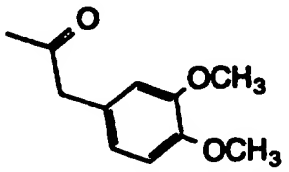
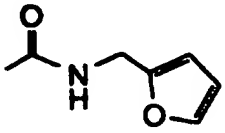
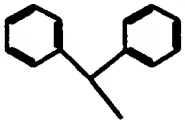
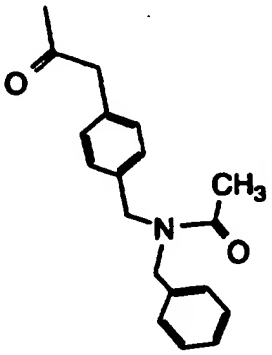
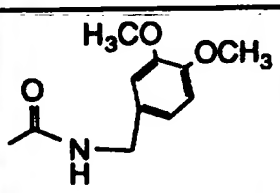
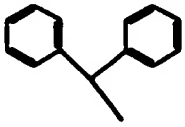
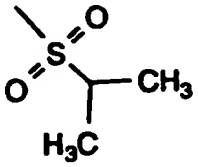
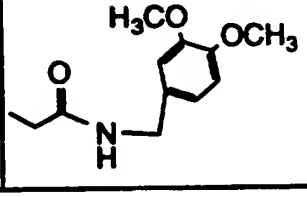
Ex. No.	Z	R1	R2
21			
22			
23			
24			
25			
26			

27			
28			
29			
30			
31			
32			

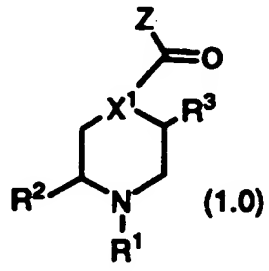
33			
34			
35			
36			
37			
38			
39			
40			

41			
42			
43			
44			
45			
46			
47			

48			
49			
50			
51			
52			

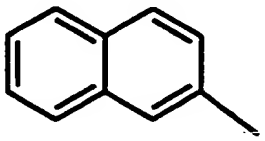
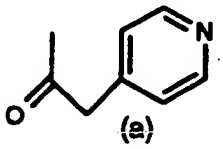
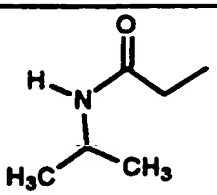
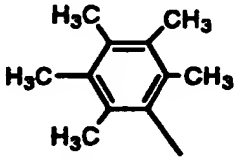
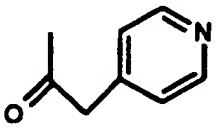
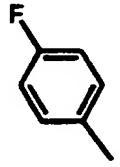
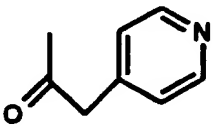
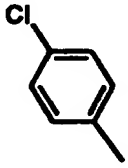
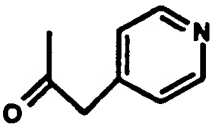
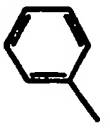
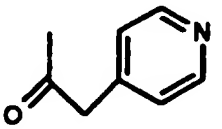
53			
54			
55			
56			
57			

FPT IC_{50} values refer to concentration, in micromoles (μM), of compound which inhibits 50% of FPT transferase.



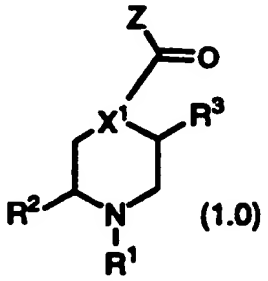
(1.0)

wherein R^3 =H

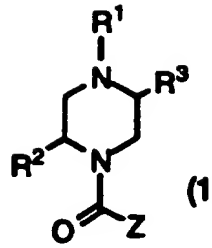
Z	X^1	R^1	R^2	FPT IC_{50} (μM)
	N	 (a)		>50
	CH		H	12.1
	CH		H	>60
	CH		H	60
	CH		H	>60

WHAT IS CLAIMED IS:

1. A compound of the formula:

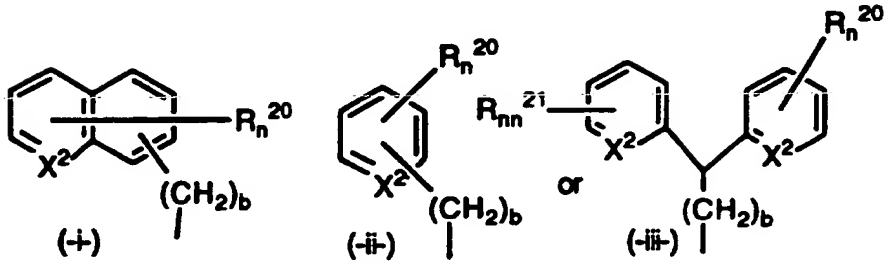

(1.0)

and


(1.1)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(1) Z is a group which is:


(-i-) (-ii-) (-iii-)

wherein X^1 is CH or N;

X^2 can be the same or different and can be CH, N or N-O;

b is 0, 1, 2, 3 or 4;

n and nn independently represent 0, 1, 2, 3, 4 or when X^2 is CH, n and nn can be 5;

R^{20} and R^{21} can be the same group or different groups when n or nn is 2, 3, 4 or 5, and can be:

(a) hydrogen, C_1 to C_6 alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, wherein each of said C_1 to C_6 alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl can be optionally substituted with one or more of the following:

C_1 to C_4 alkyl, C_3-C_6 cycloalkyl,
$(CH_2)_tOR^8$ wherein t is 0, 1, 2, 3 or 4,
$(CH_2)_tNR^8R^9$ wherein t is 0, 1, 2, 3 or 4, or
halogen;

(b) C_3 to C_6 cycloalkyl; (c) $-OR^8$; (d) $-SR^8$; (e) $-S(O)R^8$;

(f) $-SO_2R^8$; (g) $-NR^8R^9$; (h) -CN; (i) $-NO_2$,

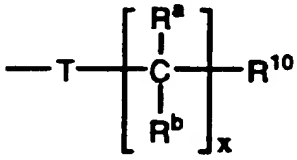
(j) $-CF_3$ or (k) halog n (l) $-CONR^8R^9$ or (m) $-COR^{13}$
wherein R^8 and R^9 can independently represent:
H, C_1 to C_4 alkyl, C_3 to C_6 cycloalkyl, heteroaryl, heteroarylalkyl, het rocycloalkyl, aryl or aralkyl and each of said alkyl, cycloalkyl, het roaryl, heteroarylalkyl, heterocycloalkyl, aryl or aralkyl can be optionally substituted with one to three of the following:

C_1 to C_4 alkoxy, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, halogen, -OH, $-C(O)R^{13}$, $-NR^{14}R^{15}$;
$-CONR^8R^9$ or $-N(R^8)COR^{13}$; -CN; C_3-C_6 cycloalkyl, $S(O)_qR^{13}$;
or C_3-C_{10} alkoxyalkoxy wherein q is 0, 1 or 2;
wherein R^{13} is selected from C_1 to C_4 alkyl, aryl or aralkyl, and
R^{14} and R^{15} are independently selected from H, C_1 to C_4 alkyl or aralkyl;

and optionally, when R^8 and R^9 are bound to the same nitrogen, R^8 and R^9, together with the nitrogen to which they are bound, can form a 5 to 7 membered heterocycloalkyl ring which may optionally contain O, NR^8, S(O)q wherein q is 0, 1 or 2;

with the proviso that R^8 is not H in substituents (e) and (f) , and with the proviso that R^8 or R^9 is not $-CH_2OH$ or $-CH_2NR^{14}R^{15}$ when R^8 or R^9 is directly attached to a heteroatom;

(2) R^1 is a group which is:



wherein

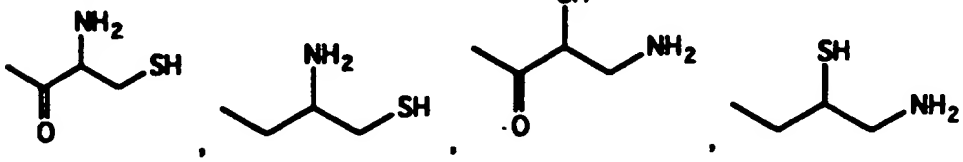
T can be , $-SO_2-$, , , or a single bond,

x = 0, 1, 2, 3, 4, 5 or 6,
R^a and R^b independently represent H, aryl, alkyl, amino, alkylamino, alkoxy, aralkyl, heterocyloalkyl, $-COOR^{16}$, $-NH(CO)_zR^{16}$ wherein z = 0 or 1, $-(CH_2)_wS(O)_mR^{16}$ wherein w=0, 1, 2 or 3 such that when x is greater than 1, then R^a and R^b can be independent of the substituents on an adjacent carbon atom provided R^a and R^b are not both selected from alkoxy, amino, alkylamino, and $-NH(CO)_zR^{16}$;
m = 0, 1 or 2 wherein
R^{16} represent H, alkyl, aryl or aralkyl,

or R^a and R^b taken togeth r can represent cycloalkyl, =O, =N-O-alkyl or heterocycloalkyl, and

R^{10} can represent H, alkyl, aryl, aryloxy, arylthio, aralkoxy, aralkthio, aralkyl, heteroaryl, het rocycloalkyl,

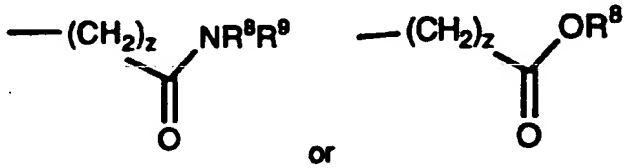
or R^1 can also be



or disulfide dimers thereof;

(3) R^2 and R^3 are independently selected from the group which is:

hydrogen, C_1 to C_8 alkyl, C_2 to C_8 alkenyl, C_2 to C_8 alkynyl,



wherein z is 0, 1, 2, 3 or 4; and said alkyl, alkenyl, or alkynyl group is optionally substituted with one or more groups which can independently represent:

(a) aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, wherein each of said aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl group can be optionally substituted with one or more of the following:

C_1 to C_4 alkyl,

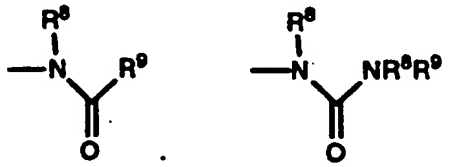
$(CH_2)_tOR^8$ wherein t is 0, 1, 2, 3 or 4,

$(CH_2)_tNR^8R^9$ wherein t is 0, 1, 2, 3 or 4, or

halogen;

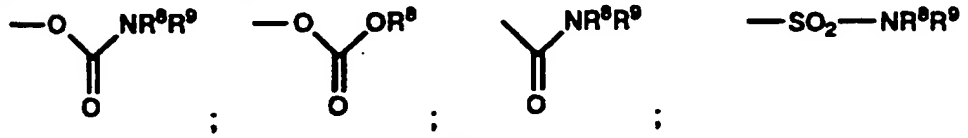
(b) C_3 to C_6 cycloalkyl; (c) $-OR^8$; (d) $-SR^8$; (e) $-S(O)R^8$;

(f) $-SO_2R^8$; (g) $-NR^8R^9$; (h) (i)

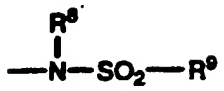
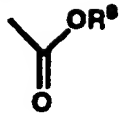
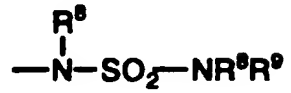


;

(j) (k) (l) (m)



;

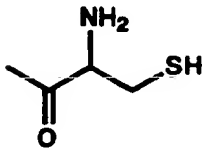
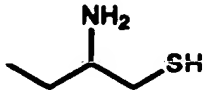
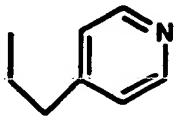
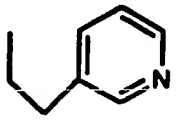
(n)  (o)  or (p) 

wherein R^8 and R^9 are defined hereinbefore; and

and optionally, when R^8 and R^9 are bound to the same nitrogen, R^8 and R^9, together with the nitrogen to which they are bound, can form a 5 to 7 membered heterocycloalkyl ring which may optionally contain O, NR^8, S(O)q wherein q is 0, 1 or 2;

with the proviso that for compound (1.0) when X^1 is CH, then R^3 is hydrogen, and with the further proviso that R^2 and R^3 cannot both be hydrogen;

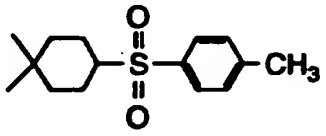
and with the provision that when X^1 is N, then R^1 is not

   or 

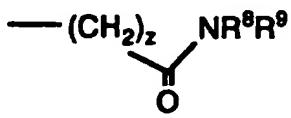
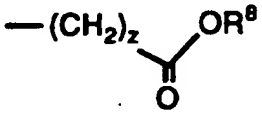
2. The compound of claim 1 wherein R^3 is hydrogen.
3. The compound of claim 1 wherein b is zero.
4. The compound of claim 1 wherein R^3 is H and b is 0.
5. The compound of claim 1 wherein Z is (-i-), (-ii-) or (-iii-), X^2 is CH or N, b=0 or 1, R^{20} is H, C1-C6 alkyl or halo, n = 0 or 1;

X^1 is N;

for R^1, T is -CO-, $-SO_2-$ or a single bond, and R^a and R^b independently represent H or C_1-C_6 alkoxy or R^a and R^b taken together can form C_3-C_6 cycloalkyl, =N-O-

C1-C6 alkyl or 

R^{10} is H, aryl, arylthio or heteroaryl;

R^2 is H,  or 

z = 0 or 1, R^8 is H and R^9 is alkyl, cycloalkyl, aralkyl, heterocycloalkyl or substituted alkyl; and

R^3 is hydrogen.

6. A pharmaceutical composition for inhibiting the abnormal growth f cells comprising an effective amount f compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

7. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of claim 1.

8. The method of Claim 7 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

9. The method of Claim 7 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

10. The method of Claim 7 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

11. The method of Claim 7 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 96/04169

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/06 A61K31/495 C07D401/12 C07D295/12 C07D241/04
C07D401/14 C07D405/12 A61K31/44 C07D409/06 C07D417/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 00497 (MERCK & CO) 5 January 1995 cited in the application see claim 1	1-11
E	WO,A,96 10035 (MERCK & CO.) 4 April 1996 see claim 1	1-11
P,X	WO,A,96 06609 (MERCK & CO.) 7 March 1996 see claim 1	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 1996	14.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Int onal Application No
PCT/US 96/04169

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9500497	05-01-95	AU-B-	7041294	17-01-95
		CA-A-	2165176	05-01-95
		EP-A-	0703905	03-04-96
WO-A-9610035	04-04-96	AU-B-	3731295	19-04-96
WO-A-9606609	07-03-96	AU-B-	3373195	22-03-96